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Activity of Monkey Frontal Eye Field Neurons Projecting to Oculomotor Regions of the Pons

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SUMMARY AND CONCLUSIONS

1. This study identified neurons in the rhesus monkey's frontal eye field that projected to oculomotor regions of the pons and characterized the signals sent by these neurons from frontal eye field to pons.

2. In two behaving rhesus monkeys, frontal eye field neurons projecting to the pons were identified via antidromic excitation by a stimulating microelectrode whose tip was centered in or near the omnipause region of the pontine raphe. This stimulation site corresponded to the nucleus raphe interpositus (RIP). In addition, electrical stimulation of the frontal eye field was used to demonstrate the effects of frontal eye field input on neurons in the omnipause region and surrounding paramedian pontine reticular formation (PPRF).

3. Twenty-five corticopontine neurons were identified and characterized. Most frontal eye field neurons projecting to the pons were either movement neurons, firing in association with saccadic eye movements (48%), or foveal neurons responsive to visual stimulation of the fovea combined with activity related to fixation (28%). Corticopontine movement neurons fired before, during, and after saccades made within a restricted movement field.

4. The activity of identified corticopontine neurons was very similar to the activity of neurons antidromically excited from the superior colliculus where 59% had movement related activity, and 22% had foveal and fixation related activity.

5. High-intensity, short-duration electrical stimulation of the frontal eye field caused omnipause neurons to stop firing. The cessation in firing appeared to be immediate, within ≤5 ms. The time that the omnipause neuron remained quiet depended on the intensity of the cortical stimulus and lasted up to 30 ms after a train of three stimulus pulses lasting a total of 6 ms at an intensity of 1,000 μA. Low-intensity, longer duration electrical stimuli (24 pulses, 75 μA, 70 ms) traditionally used to evoke saccades from the frontal eye field were also followed by a cessation in omnipause neuron firing, but only after a delay of ~30 ms. For these stimuli, the omnipause neuron resumed firing when the stimulus was turned off.

6. The same stimuli that caused omnipause neurons to stop firing excited burst neurons in the PPRF. The latency to excitation ranged from 4.2 to 9.8 ms, suggesting that there is at least one additional neuron between frontal eye field neurons and burst neurons in the PPRF.

7. The present study confirms and extends the results of previous work, with the use of retrograde and anterograde tracers, demonstrating direct projections from the frontal eye field to the pons. This direct pathway gives the frontal eye field short-latency access to oculomotor centers just a few synapses away from oculomotoneurons.

8. The frontal eye field sends a movement-related message in parallel to the superior colliculus and the pons. This message provides information about the amplitude and direction of impending saccades (where) and about both the maintenance of fixation and the release of fixation before the beginning of a saccade (when).

INTRODUCTION

The frontal eye field is critically involved in the neural processes underlying the generation of purposive eye movements (for review see Goldberg and Segraves 1989). Since Ferrier's observations in the 19th century, it has been known that electrical stimulation of the frontal lobe causes contralateral eye movements (Ferrier 1875), and more recent experiments with awake monkeys have shown that the eye movements evoked from the frontal eye field by electrical stimulation are true saccades (Robinson and Fuchs 1969). Neurons in the frontal eye field discharge before purposive saccades, even those made in the absence of visual stimuli (Bruce and Goldberg 1985). Monkeys with lesions of the frontal eye field are at first unable to make saccades into the field contralateral to the lesion, but they soon recover (Schiller et al. 1980). However, they remain unable to make certain types of cognitively difficult saccades. For example, they have a severe deficit in the learning and performance of saccades to remembered targets (Deng et al. 1986). Humans with prefrontal cortical lesions that include the frontal eye field have difficulty making saccades away from visual stimuli (Guitton et al. 1985).

The monkey's frontal eye field projects directly to oculomotor regions of the pons. The targets of these projections include the region of omnipause neurons in the nucleus raphe interpositus (RIP), the paramedian pontine reticular formation (PPRF), and cerebellar relays in the nucleus reticularis tegmenti pontis (NRTP) and basal pontine nuclei (Huerta et al. 1986; Leichnetz et al. 1984; Schnyder et al. 1985; Stanton et al. 1988b). All of these targets are important for the generation of eye movements. Omnipause neurons play a crucial role in the initiation of saccades. The cessation of their high tonic firing 10–15 ms, before the start of a saccade, enables the saccade generating mechanism to proceed (Henn and Cohen 1976; Keller 1974; Luschei and Fuchs 1972; Robinson 1975). Omnipause neurons inhibit burst neurons in the PPRF. When this inhibition is released, burst neurons generate the pulse of activity required by oculomotoneurons to drive the eye to a new location at high velocity (Luschei and Fuchs 1972; Keller 1974). Oculomotor inputs to the cerebellum are used to monitor and regulate saccadic performance (for review, see Keller 1989). Characterization of the signals carried by projections to this region can provide unprecedented insight into how the prefrontal cortex helps to control eye movements.

In this study, we have used stimulating microelectrodes centered in the omnipause region to antidromically excite neurons in the frontal eye field. This has enabled us to test the activity of identified corticopontine neurons during the performance of visuomotor tasks. We also examined the excitatory and inhibitory effects of electrical stimulation of the frontal eye field on omnipause neurons and on neurons in the adjacent PPRF. Preliminary reports of these experiments have been published elsewhere (Segraves 1991, 1992).

METHODS

Two adult rhesus monkeys (*Macaca mulatta*) were used for these experiments. All procedures for *monkey LSR51* were performed at the Laboratory of Sensorimotor Research, National Eye Institute, Bethesda, MD. Procedures for *monkey MAS01* were performed at Northwestern University.

Preoperative training

The monkeys were trained preoperatively to do a simple visual fixation task with established techniques (Wurtz 1969). The monkey was seated in a primate chair and began a trial by pressing a metal bar in front of him. This resulted in the onset of a spot of light on a screen in front of the monkey. The monkey was required to detect the dimming of the light and signal this detection by releasing the metal bar to receive a liquid reward.

Surgery

Surgery was performed under aseptic conditions. Each monkey was given an injection of ketamine hydrochloride (10 mg/kg im) to provide chemical restraint and analgesia during the preparation of the surgical area (hair clipping, etc.) and the insertion of an intravenous catheter. *Monkey LSR51* was anesthetized with intravenous pentobarbital sodium given to effect and supplemented as needed. For *monkey MAS01*, anesthesia was induced with an intravenous injection of the short-acting barbiturate sodium thiamylal, and anesthesia was maintained with halothane inhaled through an endotracheal tube. During the surgical procedure, a subconjunctival wire coil for the measurement of eye position with the magnetic search coil technique was implanted in one eye (Judge et al. 1980; Robinson 1963). Trephine holes were made through the skull to allow access by microelectrode to the frontal eye field and pons. Stainless steel bolts, to strengthen the bond of dental acrylic to the skull, were fastened in slots cut through the skull and extending away from the edges of the trephine holes. The recording cylinder intended for the pons was tilted at an angle of 20° from vertical in the frontal plane and centered at Horsley-Clarke level A3.0. Frontal eye field cylinders were positioned to allow penetrations that were roughly parallel to the banks of the arcuate sulcus. Recording cylinders, a steel receptacle to fix the monkey's head during recording sessions, and the connector for the eye coil were fixed in place and bonded to the skull with dental acrylic. Immediately after surgery, the monkey was given either gentamicin sulfate (5 mg/kg im) or cephalothin (15 mg/kg im) as a prophylactic measure against infection. The monkey received daily dosages of antibiotic for 1 wk postoperatively. Analgesic medication (buprenorphine HCl) was administered at the end of surgery and as needed for 3–4 days after surgery.

Postoperative training

Postoperative training was begun 10–14 days after surgery. Each monkey received training in several visuomotor tasks. The computer hardware and software used to monitor and control the monkey's behavior has been described in detail elsewhere (Goldberg 1983). Briefly, the monkey was seated in a primate chair with its head fixed and centered within horizontal and vertical magnetic field coils. All behavioral control and data collection was performed via interfaces with the laboratory computer (PDP-11/73, Digital Equipment). Visual stimuli presented to the monkey included stationary and movable light stimuli originating from light-emitting diodes rear-projected onto a tangent screen in front of the monkey. The movable stimulus was positioned by a pair of servo-controlled mirror galvanometers (General Scanner) driven by computer generated analog signals. The room in which the monkey performed these tasks was dimly lit. Because it was possible to measure eye position after surgery, the monkey was no longer required to detect the dimming of the stimulus. Instead, the monkey had to meet predetermined criteria for eye position relative to stimulus position, or for saccade amplitude and direction to receive a liquid reward. Eye position was measured by the magnetic search coil system with a phase-sensitive detector (C.N.C. Engineering).

Visuomotor tasks

Each task began with the appearance of a central stationary light on the screen. The computer monitored the monkey's eye position, and after the monkey maintained fixation of the central light for 100 ms, the computer began the timing intervals of the task at hand.

1) *Fixation task*. The monkey was required to hold fixation throughout the trial. During some trials the fixation light was turned off at an unpredictable moment for a brief period of time. The monkey was rewarded for maintaining eye position within a window surrounding the fixation point such that the sum of the horizontal and vertical differences between eye and target position was <5° (Sparks and Holland 1975). This was a criterion that the monkeys met easily and usually surpassed. With practice each monkey was able to maintain fixation of the target's initial position throughout the trial, including periods when the light was turned off. This paradigm enabled us to test the effects of visual stimulation of the fovea on neuronal activity, as well as the relationship of a neuron's activity to visual fixation.

2) *Visual no-saccade task*. The monkey fixated the stationary light spot in the center of the tangent screen for the duration of the trial. At an unpredictable moment during the trial, a second light spot was flashed for a variable period of time. The position of the second light was controlled by mirror galvanometers and could be placed anywhere within the monkey's visual field. This stimulus was used to map visual receptive fields. Because the monkey was rewarded for maintaining fixation of the center light throughout the trial, the peripheral stimulus had no behavioral significance.

3) *Visually guided saccade task*. After a variable period of fixation, the center light was extinguished at the same moment that a peripheral target light was turned on. When the peripheral target appeared, the monkey was required to make a saccade to the target's location within 500 ms. After the saccade, the monkey was rewarded either for maintaining eye position within a window with ~3–6° radius surrounding the new target position or for having made a saccade whose end point was within this window. The movable light spot was again used for the peripheral target and could be positioned anywhere on the tangent screen.

4) *Memory guided saccade task*. In a second more difficult form of saccade task, the center light came on to start the trial, as before, and the monkey was required to begin and maintain fixation of the center light until it was turned off. During the central fixation period, a peripheral target was turned on for 50–300 ms. When the center light was turned off, the monkey was required to make a saccade to the position of the flashed peripheral target light. The duration and time of occurrence of the target flash were

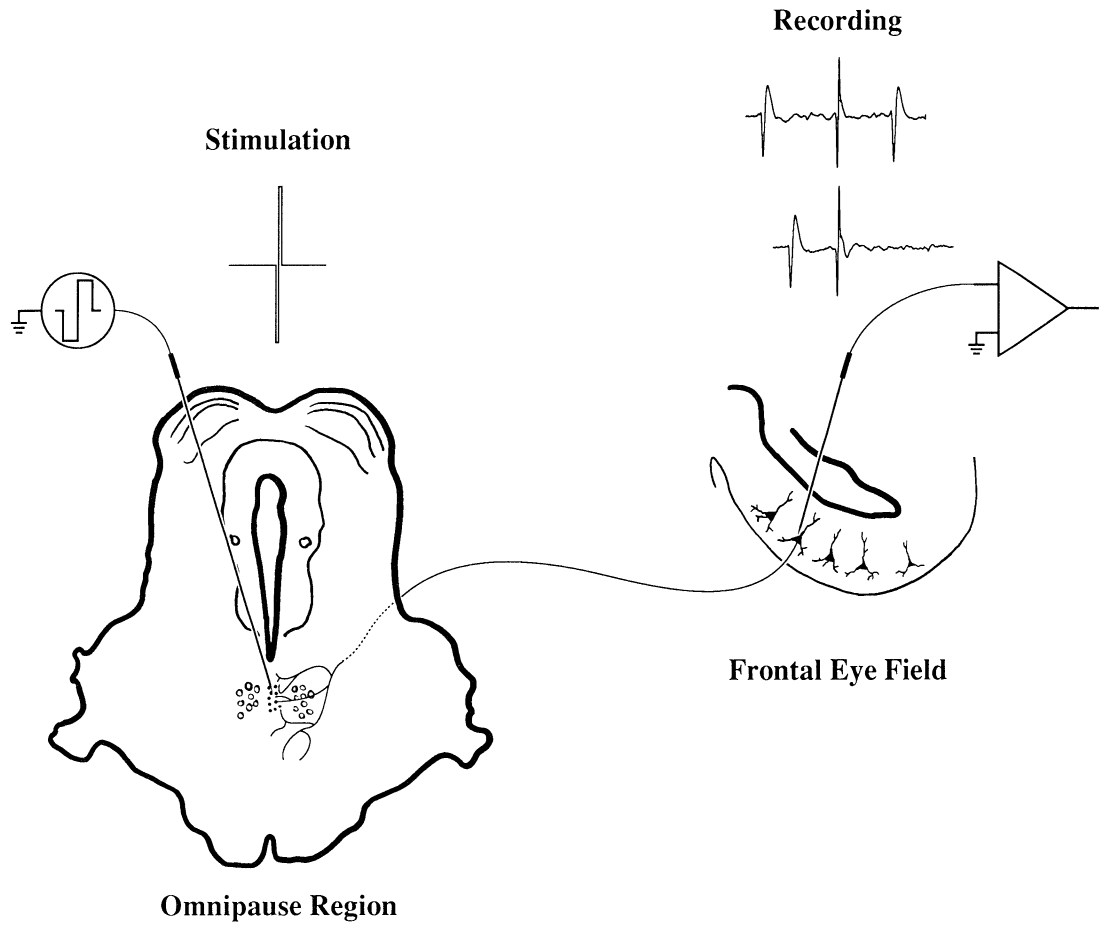

FIG. 1. Recording and stimulation setup. Single neurons isolated by a microelectrode in the frontal eye field were antidromically excited by a monopolar stimulating microelectrode whose tip was positioned within the omnipause region of the pons. Recording traces included here are described in detail in Fig. 3.

adjusted so that the target light was turned off during the fixation period, requiring the monkey to maintain fixation for ≤250 ms after the target light's disappearance, and then make a saccade to a remembered target location. This task enabled us to distinguish between visual- and movement-associated neuronal activity during the trial.

In this study, the location of visual stimuli and targets are expressed in polar coordinates, radius and angle, where radius is equal to the distance in degrees of arc of the target or stimulus from the fixation point. An angle of 0° describes a rightward horizontal direction, and a 90° angle describes an upward vertical direction.

Electrophysiology

The electrophysiological techniques employed in these experiments are similar to those employed in a previously reported study of frontal eye field neurons that project to the superior colliculus (Segraves and Goldberg 1987). Frontal eye field neurons were antidromically excited via stimulation through microelectrodes positioned in the pons. A diagram of the stimulation and recording set-up is provided in Fig. 1 illustrating the antidromic excitation of a single neuron in the frontal eye field by a monopolar stimulating electrode in the omnipause region of the pons.

Single-unit recordings were made with tungsten microelectrodes. With two hydraulic microdrives (Narishige, Japan), the tip of one electrode was positioned within the frontal eye field. The tip of the other electrode was positioned in the pons. For penetrations into the pons, we used a 23-gauge guide-tube that passed through dura and cortex and whose tip was positioned several millimeters above the surface of the superior colliculus. The topographic map of the superior colliculus was used as an aide in positioning the pontine electrode (Cynader and Berman 1972; Robinson 1972; Schiller and Stryker 1972). Electrode penetrations directed at the frontal eye field were made either directly through the dura mater, or through guide tubes, which passed through dura only. A plastic grid placed within the recording cylinder was used as an aide in the positioning of electrodes and guide tubes (Crist et al. 1988). When a guide tube was not in use, a wire matched to the inside diameter of the 23-gauge tubing and coated with antibiotic (3% tetracycline HCl ointment) was inserted into it. Discrimination of the action potentials of single neurons from the extracellular recording signal was done with a conventional time/amplitude window discriminator (Bak Electronics, Rockville, MD) for *monkey LSR51*. For *monkey MAS01*, action potential discrimination was done with a computer-based waveform discriminator (Signal Processing Systems, Prospect, Australia).

We used several criteria to define areas used for recording and stimulation. The frontal eye field was defined as the area of cortex, located primarily on the rostral bank and fundus of the arcuate sulcus, where eye movements could be evoked with thresholds of 50 μA or less (Bruce and Goldberg 1985; Bruce et al. 1985.). The electrode directed at the pons passed through superior and inferior colliculi as well as lateral portions of the PPRF before arriving in the region of omnipause neurons between the rootlets of the 6th cranial nerve near the midline pontine raphe. Omnipause neurons were identified by their high tonic firing rate, which stopped 10–15 ms before the beginning of saccades in any direction (Fig. 2).

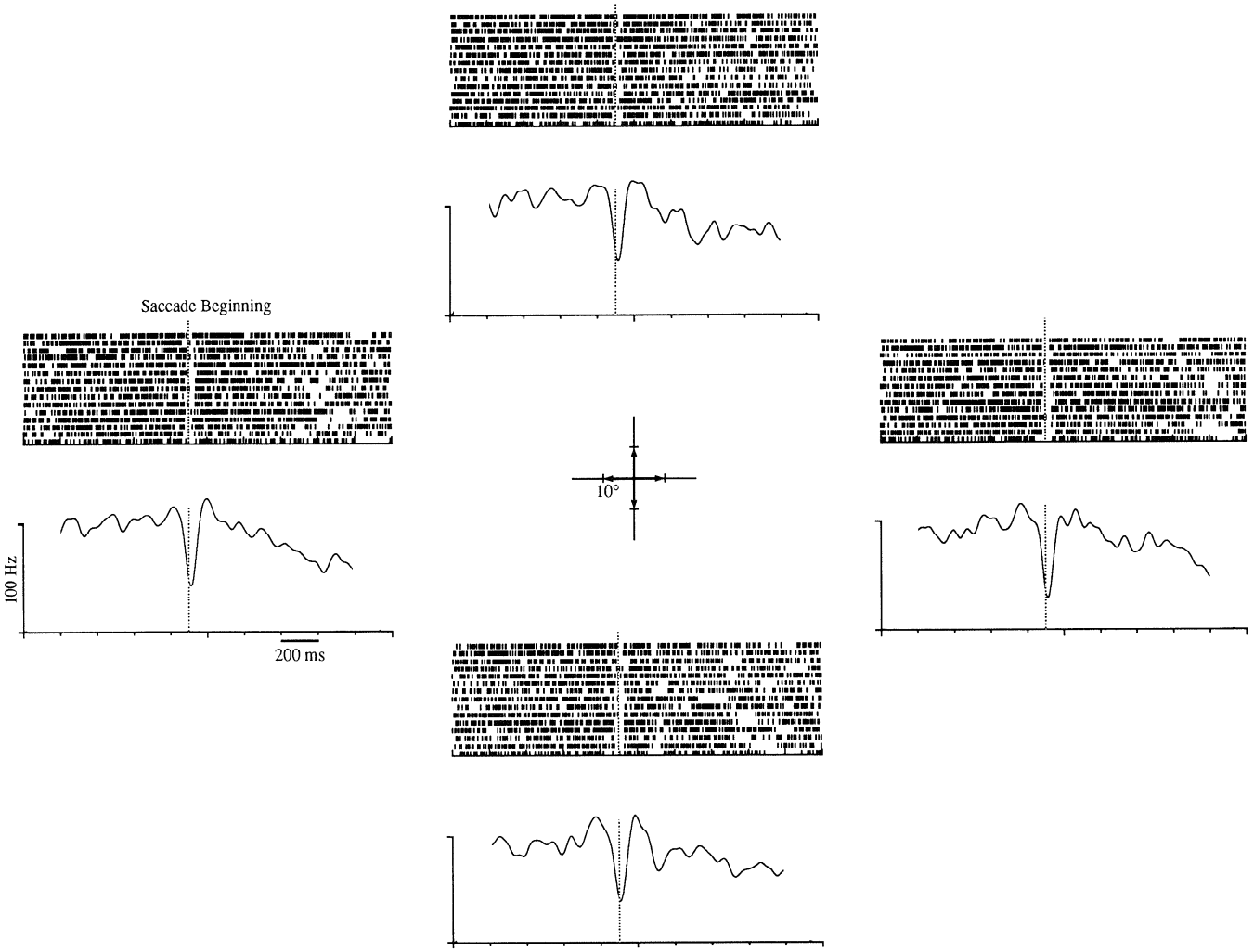

FIG. 2. Omnipause neuron activity recorded at a pontine stimulation site. Activity from this omnipause site was recorded before applying stimulus pulses through the microelectrode to antidromically excite frontal eye field neurons. The 4 quadrants of the figure represent the activity associated with 10° saccades made in 4 directions. Each quadrant represents activity in raster and spike-density forms. Each small raster tick represents 1 neuron spike (sampled at 250 Hz), every raster line includes the neuron activity from a 2-s interval of a single trial. To generate the spike-density profile, a Gaussian curve with $\sigma = 5$ ms was fitted to the time of occurrence of each neuron spike. For each trial, Gaussian curves representing each spike were summed, providing a continuous function expressing the expected spike frequency for any point in time during the trial. Spike-density profiles for successive trials were then averaged to produce the profiles included in this and subsequent figures. For this neuron, the expected firing rate was ~100 Hz. The vertical line passing through both raster and spike-density profile is the point of alignment for the activity, in this case, the beginning of the saccade.

Omnipause neurons stopped their tonic firing when the monkey became drowsy and began to sleep (Henn et al. 1984). They were distinguished from pause neurons with directional preferences found dorso-lateral to omnipause neurons corresponding to the directional pause neurons with vestibular inputs described by Raybourn and Keller (1977). These latter neurons tended to have lower firing rates, paused for some directions of eye movements but not others, and were not affected by whether the monkey was awake or asleep. The omnipause region has been characterized anatomically by Büttner-Ennever and colleagues (1988) and has been named the RIP. The frontal eye field projects directly to this region (Huerta et al. 1986; Schnyder et al. 1985; Stanton et al. 1988a,b). These projections, as well as the frontal eye field's projections to more lateral parts of the PPRF and to the NRTP, are bilateral.

Antidromic excitation was used to identify cortical neurons projecting to the pons. We searched for frontal eye field corticopontine neurons by stimulating through the pontine electrode after each 50- to 100-μm movement along the penetration through cortex. During these penetrations, the activity of neurons during visuomotor tasks was also observed to monitor the progress of the penetration through cortex, but in no case was the activity of a neuron used as a criteria for testing to see if it projected to the pons. At each site, we first applied pontine stimuli to see if neurons could be antidromically excited, then we examined the activity of the neurons during visuomotor behavior. All of the identified classes of frontal eye field neurons were encountered during these penetrations (Bruce and Goldberg 1985).

Stimulation through the pontine electrode to antidromically excite frontal eye field neurons was done with biphasic negative first pulses 0.2 ms in duration. The output of the stimulus generator (Grass S88) was connected to the electrode through constant-current optical isolators (Grass PSIU6). The level of stimulus current was determined from the voltage measured across a 1-kΩ resistor in series with the electrode. Searching for antidromically excitable neurons was routinely done with stimulus currents of 1

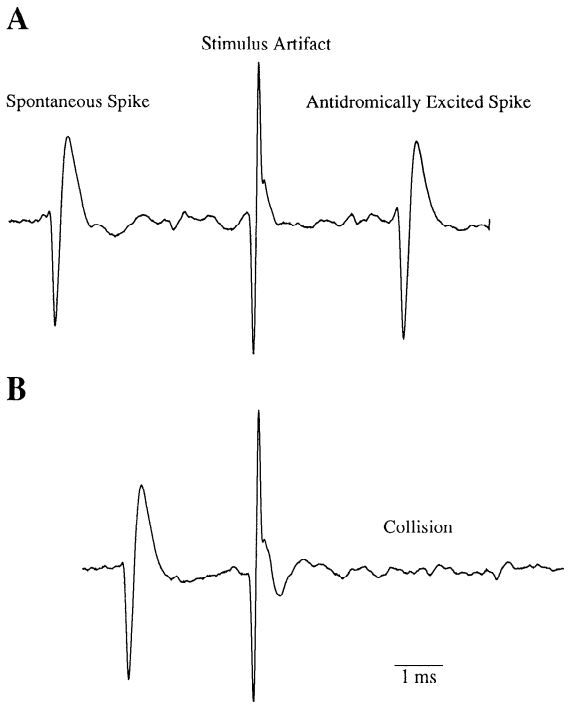

FIG. 3. Example of antidromic excitation, collision. Both traces begin with the occurrence of a spontaneous spike generated by a neuron isolated in the frontal eye field. Traces are aligned on the pontine stimulus artifact. When the spontaneous spike and pontine stimulation were separated by 4 ms (*A*), the neuron was antidromically excited with a latency of 3 ms. When the separation between spontaneous spike and stimulus was reduced to 2.6 ms (*B*), the antidromically evoked spike collided with the spontaneous spike and was not seen at the frontal eye field electrode. Stimulus intensity, 500 μA.

mA, and stimulus intensity never exceeded this level. Once an antidromically excitable neuron was isolated, its excitation threshold was determined, and the stimulus current was then set to a level 50% greater than threshold. We defined threshold as the current intensity at which antidromic spikes were obtained in response to ~50% of the stimulus pulses. Antidromically excited neuronal responses were identified by their fixed latency and by our ability to collide the neuronal spike with spontaneous spikes originating in the frontal eye field (Bishop et al. 1962; Fuller and Schlag 1976). Figure 3 shows an example of the antidromic excitation and collision of a frontal eye field neuron by stimulation of the omnipause region.

The effects of electrical stimulation of the frontal eye field on neurons isolated by the pontine electrode was tested with stimulus trains of one to four biphasic pulses administered at 330 Hz. Stimulus current was ≤1 mA.

To evoke saccades, 330-Hz trains of pulses were administered through the cortical electrode. Train duration was 70 ms with current strength ≤75 μA.

None of the electrical stimuli used were aversive. The monkey remained in a relaxed state during their administration, and frequently fell asleep during periods when electrical stimuli were being applied if no behavioral task was being run.

Behavioral and neuronal activity were sampled at 1 kHz. These data were stored temporarily in the laboratory computer, then transferred to a UNIX-based workstation (Sun Microsystems) for off-line analysis.

Data Analysis

We classified neurons on the basis of their activity during visuomotor tasks, with the criteria of Bruce and Goldberg (1985). Rasters and histograms were constructed with neuron activity aligned on important events within a trial. Neuronal activity was also plotted as continuous spike-density functions (Richmond et al. 1987; Sanderson and Kobler 1976). A Gaussian curve with $\sigma = 5$ ms was fitted to the time of occurrence of each neuron spike. For each trial, Gaussian curves representing each spike were summed, providing a continuous function expressing the expected spike frequency for any point in time during the trial. Spike-density functions for successive trials were then averaged to produce the spike-density profiles included in the figures.

Histology

One to two weeks before the end of the experiment, marking lesions were made at the locations of a few antidromically excited neurons in the frontal eye field, as well as at the low threshold pontine sites from which these neurons could be antidromically excited. At the conclusion of the experiment, the monkeys were given a lethal dose of pentobarbital sodium and perfused transcardially with saline followed by either a mixture of 4% paraformaldehyde and 0.1% glutaraldehyde (*LSR51*) or with 10% Formalin. The brains were then removed, photographed, and frozen sectioned at 50 μm. Two planes of section were used (see Fig. 4). Sections through the midbrain and pons were made in the frontal plane. Sections through the arcuate sulcus were made in a plane running rostrocaudally, parallel to the principal sulcus. For both brains, sections were mounted and stained with cresyl violet. For *LSR51*, a series of sections through the midbrain and pons were stained for cytochrome oxidase (Wong-Riley 1979). Cytochrome oxidase staining was used to confirm the location of the RIP on the basis of the criteria of Büttner-Ennever and colleagues (1988).

RESULTS

A total of 25 frontal eye field neurons were antidromically excited with pontine stimulation and were isolated for a sufficient period of time to have their activity characterized during the monkey's performance of several visuomotor tasks. These identified and characterized neurons include 9 neurons from the right frontal eye field of *monkey LSR51* and 16 neurons from the right frontal eye field of *monkey MAS01*.

Figure 4 illustrates the recording and stimulation sites for a corticopontine neuron. This neuron was located on the anterior bank of the right arcuate sulcus (Fig. 4*A*). It was antidromically excited from the pons with a latency of 1.4 ms and a threshold of 350 μA. The lesion marking the recording site straddles cortical layers V and VI. Strong movement related activity was recorded both from the antidromically excited neuron as well as from adjacent neurons at this site. Three lesions, spaced at 1-mm intervals, were used to mark the stimulation site in the pons (Fig. 4*B*). The actual stimulation site is marked by the lowest of the three lesions, which is located slightly to the right of the midline and centered within the RIP. Neurons with omnipause activity were isolated at this site. At the two lesion sites located 1 and 2 mm above the stimulation site, neurons bursting before leftward saccades were isolated.

Activity of antidromically excited neurons in visuomotor tasks

The distribution by activity type of identified corticopontine neurons from each monkey is listed in Table 1.

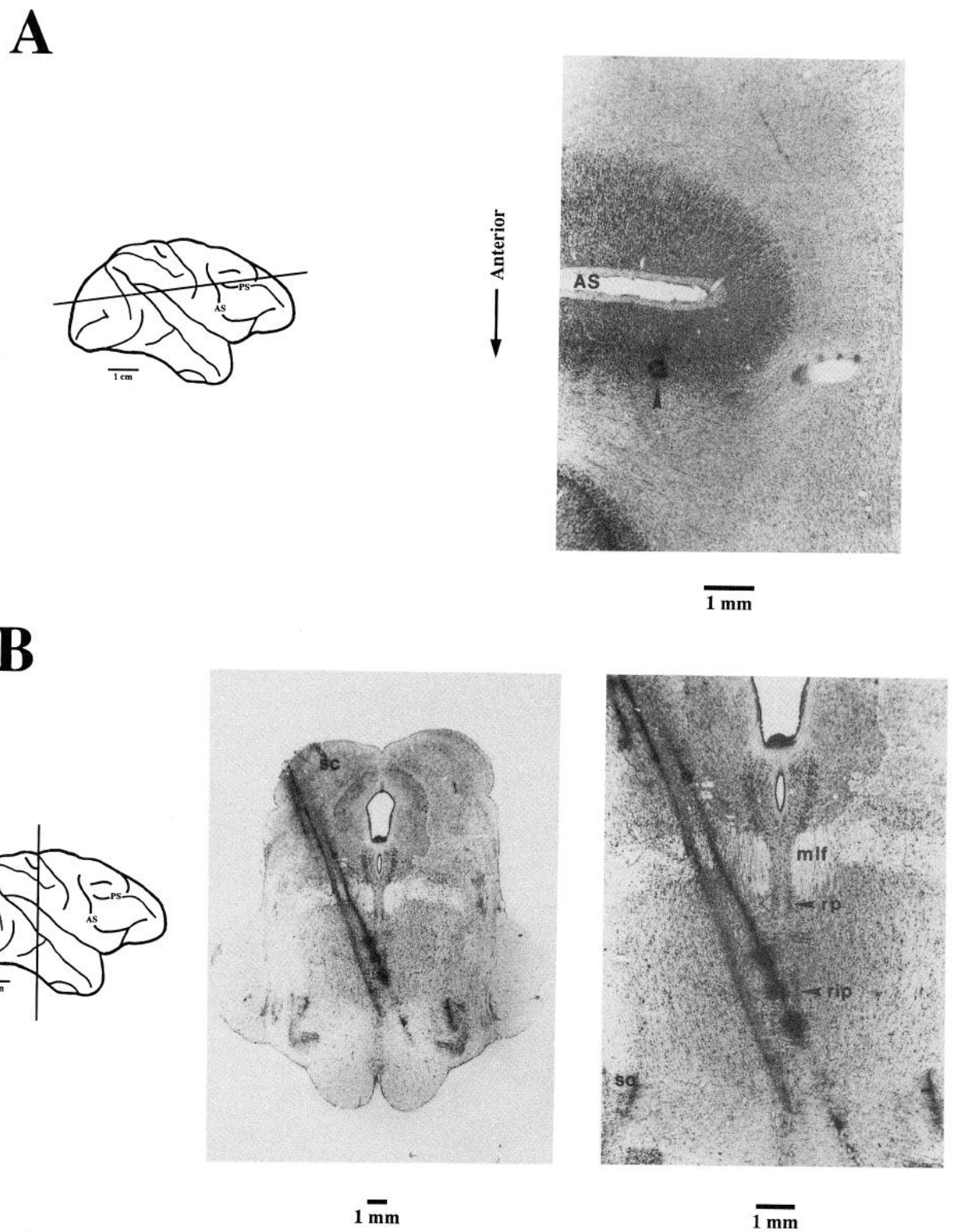

FIG. 4. Recording and stimulation sites for a corticopontine neuron. *A*: recording site for antidromically excited neuron in the right frontal eye field of monkey MAS01. The lesion (indicated by arrowhead) is located on the anterior bank of the arcuate sulcus (AS). This section was made in a plane that was roughly parallel to the principal sulcus (PS). The hole in the white matter, near the fundus of the arcuate sulcus, was made by a marking pin inserted at the time the monkey was perfused. *B*: stimulation site for antidromic excitation of neuron at cortical site shown in *A*. This section was made in the frontal plane and is located at an approximate Horsley-Clark level of APO–PO.5. Three lesions were made, spaced at 1 mm intervals, near the midline of the pons. The lowest of the 3 lesions, located slightly to the right of the midline and within the RIP, marks the stimulation site for antidromic excitation of the corticopontine neuron localized in *A*. mlf, medial longitudinal fasciculus; rp, nucleus raphe pontis; rip, nucleus raphe interpositus; sc, superior colliculus; so, superior olive.

TABLE 1. *Distribution of corticopontine neuron activity*

Activity Type	*Monkey LSR51*	*Monkey MAS01*	Total	Percent of Total
Visual	0	0	0	0
Visuomovement	0	0	0	0
Movement	4	8	12	48
Postsaccadic	0	0	0	0
Foveal	1	6	7	28
Eye position	4	0	4	16
Others	0	2	2	8
Nonresponsive	0	0	0	0
Totals	9	16	25	100

Distribution of activity types for neurons antidromically excited from the pons. The number of neurons in each activity category are shown for each monkey, as well as the total for both monkeys.

MOVEMENT NEURONS. Forty-eight percent (n = 12) of the antidromically excitable neurons that were identified and characterized in this study belonged to the movement class of frontal eye field neurons. These neurons yielded little or no response to visual stimuli but were very active before, during, and after visually guided and memory guided saccades. Their activity peaked at about the time that the saccade began. They had definable movement fields, being most active in association with saccades of a specific amplitude and direction. They gave little or no discharge, however, before spontaneous saccades of the appropriate direction made in the dark. They did not discharge in response to visual stimulation of the fovea. An example of an antidromically excited movement neuron is shown in Fig. 5. Activity was recorded during the monkey's performance of a visually guided saccade task. This neuron began to fire ~200 ms after the target light appeared (Fig. 5*A*). Its firing peaked just when the saccade began (Fig. 5*B*) and ended within 100 ms after the end of the saccade (Fig. 5*C*). The movement field for this neuron was centered at 15° radius and 180° angle, on the horizontal meridian in contralateral space. This neuron was not active in tasks that did not require saccadic eye movements, including tasks requiring fixation alone or smooth pursuit eye movements. It did not fire in response to visual stimuli presented within the area encompassed by its movement field. Its firing was tied to the performance of a saccade.

The optimal saccade vectors for corticopontine movement neurons included in this study are shown in Fig. 6. Amplitudes ranged from 7 to 30°. Directions covered a wide range of contralateral space and, for two neurons, included optimal saccade vectors directed ipsilaterally. One neuron fired before saccades made in all directions.

FOVEAL NEURONS. Twenty-eight percent (n = 7) of the identified corticopontine neurons were classified as foveal neurons. Foveal neurons responded to visual stimulation of the fovea. They were either excited or suppressed by foveal light stimuli and discharged most strongly in our saccade tasks either during attentive fixation or at the disappearance of the fixation point, signaling the time to make a saccade. Figures 7 and 8 illustrate an example of a foveal neuron that was antidromically excited by pontine stimulation. In a fixation task (Fig. 7), the neuron began firing shortly after the appearance of the fixation point at the beginning of the trial (Fig. 7*A*). In this task, the monkey was free to move its eyes during a short intertrial interval of 500 ms. Normally, the monkey kept its eyes close to the center of the screen and foveated the fixation point soon after it was turned on. During the trial, at an unpredictable time, the fixation point was turned off for 250–500 ms (Fig. 7*B*). The neuron stopped firing during this period and resumed firing after the reappearance of the fixation point (Fig. 7*C*).

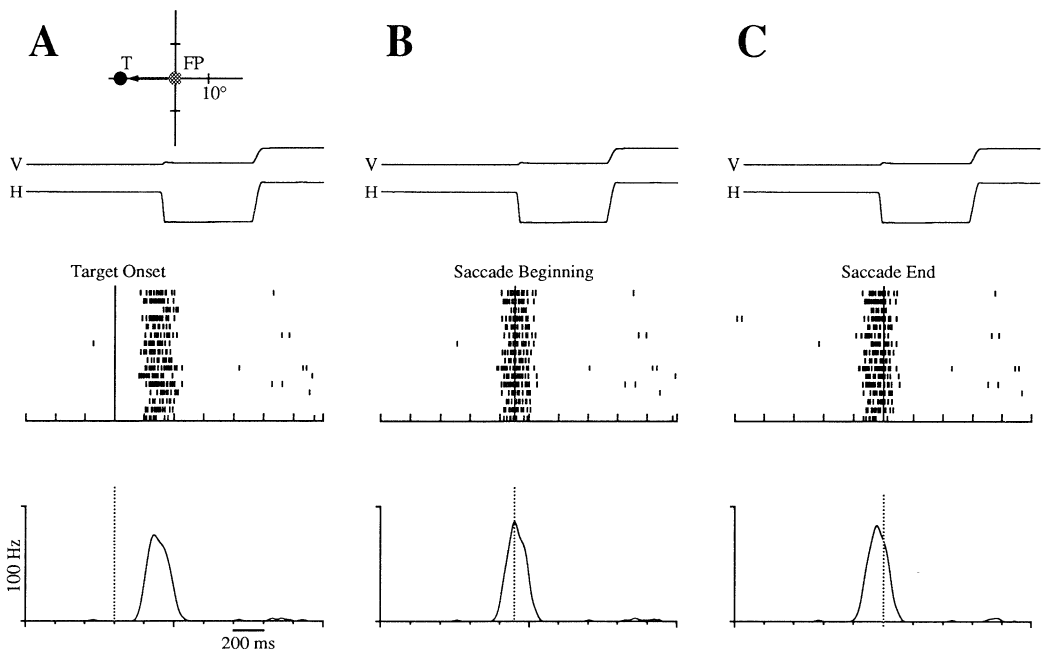

FIG. 5. Corticopontine movement neuron activity. Activity recorded during the performance of a visually guided saccade task. Saccades were made to a target (T) located 17° to the left of the initial fixation point (FP). Above each raster, vertical (V) and horizontal (H) eye position traces from a single trial are included. Rasters and spike-density profiles are aligned on the target onset (*A*), beginning of the saccade (*B*), and end of the saccade (*C*).

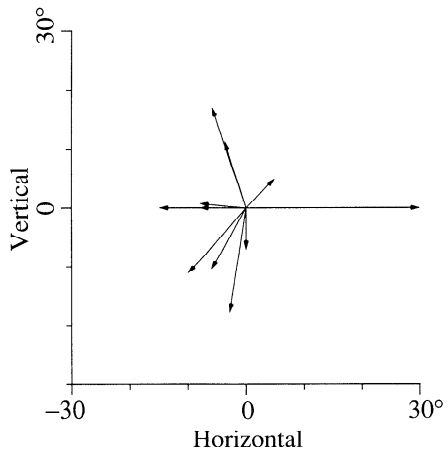

FIG. 6. Saccade vectors for identified corticopontine movement neurons. Vectors correspond to the direction and amplitude of saccades into the center of the movement fields for frontal eye field movement neurons antidromically excited from the pons. All neurons were isolated in the right cerebral hemisphere. Vectors for 11 of 12 movement neurons are included in this figure. The remaining movement neuron fired before saccades in all directions.

It stopped firing after the fixation point was turned off at the end of the trial (Fig. 7*D*). In the memory-guided saccade task (Fig. 8), this neuron was active while the monkey fixated and stopped firing after the fixation point was extinguished (Fig. 8*A*). The cessation in firing was not sensitive to the variable duration of the target flash but was closely tied to the disappearance of the fixation point. This neuron stopped firing ~100 ms before the beginning of the saccade to the remembered target location (Fig. 8*B*). All but one of the corticopontine foveal neurons was excited by visual stimulation of the fovea during the fixation task (foveal-on response). The remaining neuron was quiet during foveal visual stimulation and increased its activity when the fixation light was turned off either during or at the end of the trial (foveal-off response). Foveal neurons also tended to be active during tracking tasks involving pursuit of a visual target. It is likely that they were responding to the presence of a foveal visual stimulus rather than to the pursuit eye movements themselves.

EYE POSITION NEURONS. Four neurons were classified as eye position sensitive neurons. The tonic firing activity of these neurons was modulated by the position of the eye in the orbit. Figures 9 and 10 illustrate a neuron that preferred rightward (ipsilateral) eye positions. For this neuron, the monkey was required to fixate spots of light presented at different locations on the tangent screen (Fig. 9). When the monkey fixated a spot presented 20° to the left of the center of the screen, the neuron fired at a low tonic rate (Fig. 9*A*). When the monkey fixated a spot presented in the center of the screen, the tonic firing rate increased (Fig. 9*B*). The neuron was most active when the monkey fixated a spot located 20° to the right of the center of the screen (Fig. 9*C*). In visually guided saccade tasks (Fig. 10), the neuron increased its tonic rate when the monkey made a saccade from the center of the screen to a target presented in the right hemifield (Fig. 10*A*). The tonic rate decreased when the monkey made a saccade from a rightward eye position towards the center of the tangent screen (Fig. 10*B*). In addition to these changes in tonic firing rate, there was a transient increase in firing coinciding with the beginning of the

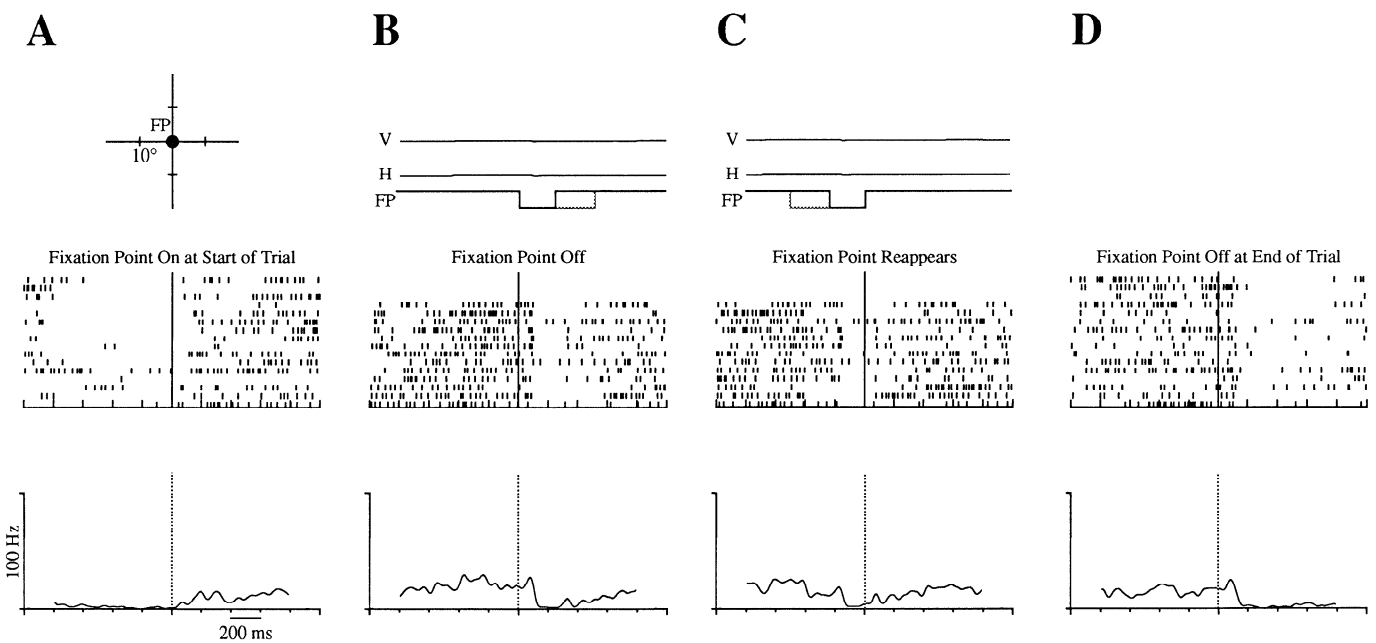

FIG. 7. Activity of corticopontine foveal neuron during fixation task. Activity aligned on 4 separate events during the trial. The monkey was required to fixate the location of a fixation light (FP) for the duration of the trial. During the trial, the fixation point was turned off for a period of 250–500 ms. The presence of the fixation light is indicated by trace FP directly below the vertical and horizontal eye position traces. Downward deflections correspond to the disappearance of the fixation light, and upward deflections correspond to its reappearance. Solid and dashed lines outline the shortest and longest times for the fixation light off-period. Rasters and spike-density profiles are aligned on the appearance of the fixation point at the beginning of the trial (*A*), the turning off (*B*) and on (*C*) of the fixation point during the trial, and its the disappearance at the end of the trial (*D*).

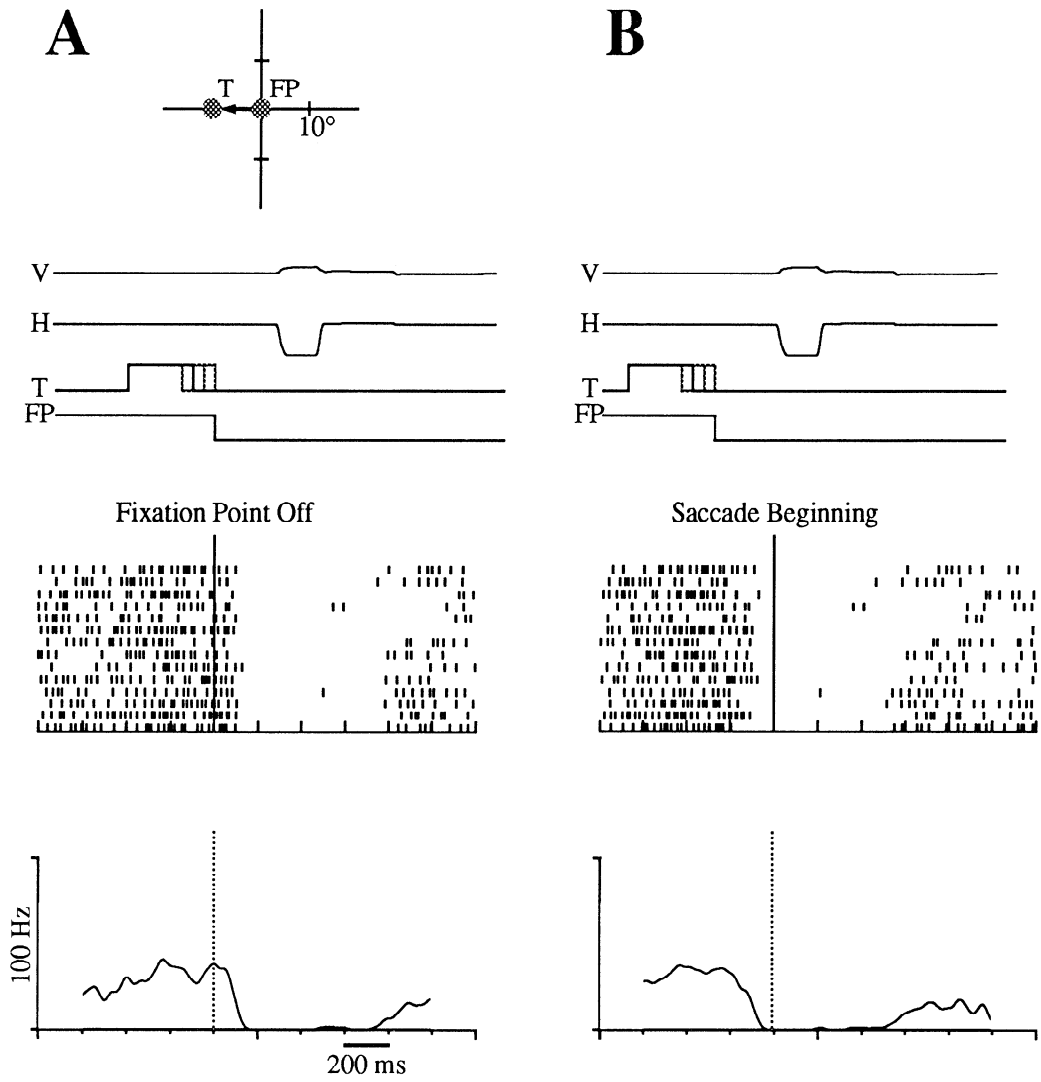

FIG. 8. Activity of corticopontine foveal neuron during memory-guided saccade task. Same neuron as in Fig. 7. In this task, a target light appeared 11° to the left of the fixation light and remained on for 250–400 ms. After the disappearance of the target, the fixation light remained on for 0–150 ms and then disappeared. The disappearance of the fixation light was the monkey's cue to make a saccade to the remembered location of the target light. For the eye position traces included in this figure, the target light was on for 300 ms followed by a delay of 100 ms before fixation light disappearance. The remaining outlines in the target light traces correspond to target light on and fixation light off delay times of 250/150, 350/50, and 400/0 ms. Rasters and spike-density profiles are aligned on the disappearance of the fixation point (*A*), and the beginning of the saccade (*B*).

saccade from center to rightward gaze, and a transient decrease in firing coinciding with the saccade from rightward gaze towards the center of the screen. Although they were found in only one of the two monkeys used for this study (*LSR51*), these four neurons were isolated at four different frontal eye field recording sites made on different days, and separated by ≤3 mm on the cortical surface. Stimulation to antidromically excite these neurons was via electrodes passed through three different pontine guide-tube locations.

OTHER NEURONS. Only two neurons in our sample of antidromically excited corticopontine neurons did not fit the classification of either movement, foveal, or eye position sensitive.

One neuron was most active while the monkey used smooth pursuit to track targets moving to the left (contralateral). It was not active during the fixation of a stationary target or during saccade tasks. In a step-ramp task where the target was stepped 15° to the right and then moved leftward with a speed of 15°/s, the neuron increased its firing before the saccade made to the moving target. This increase in firing may have been related to the initiation of leftward pursuit before the target was foveated.

Another corticopontine neuron decreased its activity in association with saccades. For visually guided saccades, the pause in this neuron's firing began ~100 ms before the beginning of saccades directed up or to the right (ipsilateral). Its activity paused at the beginning of saccades directed down or to the left (contralateral). For every direction, activity did not resume until ~100 ms after the end of the saccade.

Numerous visual, visuomovement, and postsaccadic neurons were encountered during electrode penetrations used

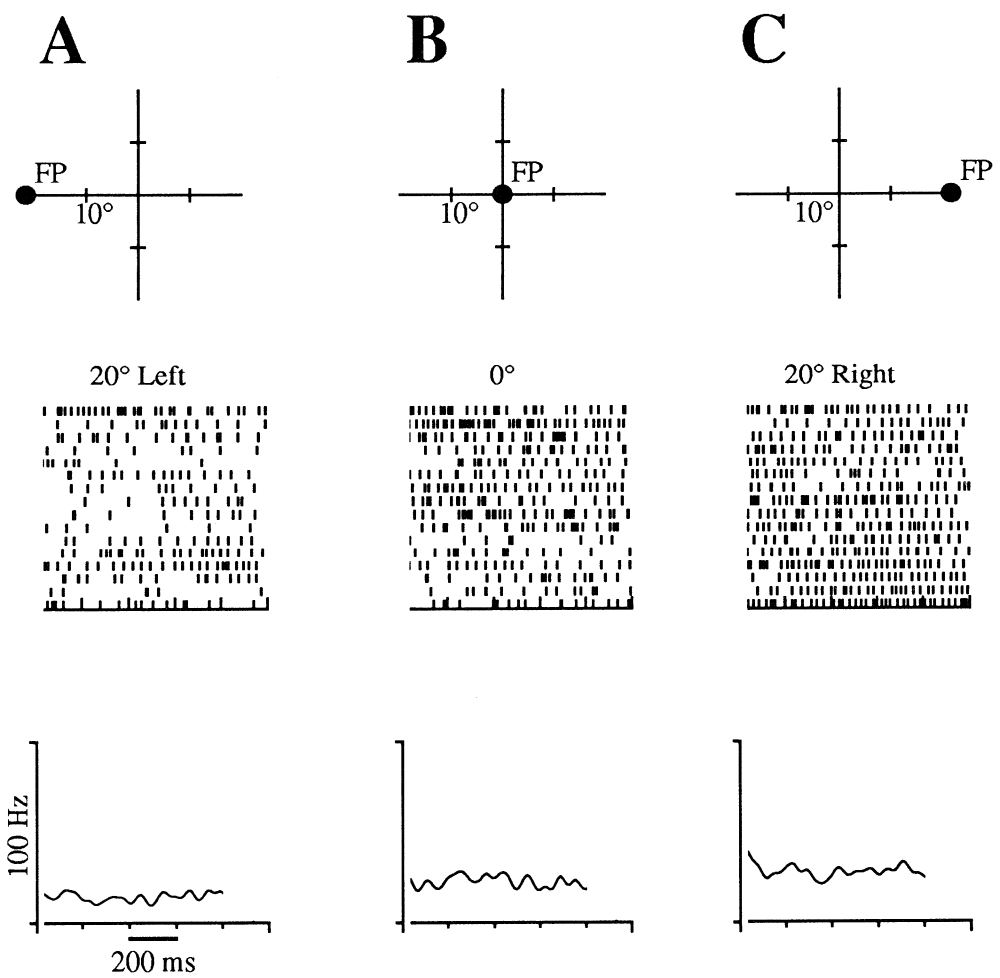

FIG. 9. Activity of corticopontine eye position sensitive neuron during fixation at different orbital positions. Activity was recorded during fixation of a light located 20° to the left of the center of the tangent screen (*A*), at the center of the tangent screen (*B*), and 20° to the right of the center of the tangent screen (*C*).

to search for antidromically excitable neurons. No members of these activity types were antidromically excited from the pons.

Antidromic latencies and thresholds

The latencies for antidromic excitation from pons to frontal eye field ranged from 0.8 to 3.4 ms (Fig. 11). The mean latency was 1.9 ms. Thresholds for antidromic excitation ranged from 10 to 600 μA (Fig. 12). Mean threshold was 277 μA.

Once an antidromically excitable neuron was isolated and the relationship of its activity to visuomotor behavior was determined, we moved the stimulating electrode in 250-μm intervals above and below the initial stimulation site to locate the site with the lowest threshold for antidromic excitation. This was done for 11 neurons. Eight of these neurons had their low-threshold site located within the region where omnipause neurons were found. For example, the movement neuron whose activity is illustrated in Fig. 5 was antidromically excited with a minimum threshold of 350 μA at the site where the omnipause neuron used for Fig. 2 was isolated. Although the stimulating electrode remained within the region where omnipause activity could be recorded, the threshold remained at 350 μA. At sites 650 μm above and 1,200 μm below the omnipause region, thresholds increased to >1,000 μA. Of the remaining three neurons tested, one neuron had a minimum threshold of 35 μA at a site located 600 μm dorsolateral to the omnipause neuron region. This site was within the left PPRF, contralateral to the cortical recording site and contained neurons with burst activity associated with leftward saccades. At 1,500 μm above this minimum threshold site, neurons still fired in association with leftward saccades, but the threshold had increased to >1,000 μA. As the stimulating electrode was moved deeper, threshold increased >1,000 μA at a location where omnipause neuron activity was recorded, 1,000 μm below the lowest threshold site. For all pontine penetrations, as the stimulating electrode was advanced through the PPRF towards the midline, omnipause neuron activity was recorded on either side of the midline. Two neurons had their minimum thresholds obtained at sites encountered 1.0–2.5 mm ventrolateral to the midline omnipause region. Anatomically, these sites would be located within the right basal pontine nuclei, ipsilateral to the cortical recording site, and possibly within a posterior portion of the NRTP. In these penetrations, as well as two subsequent penetrations made to examine the location of the stimulation sites, neurons with combinations of visual and saccade related activity were recorded after the electrode passed

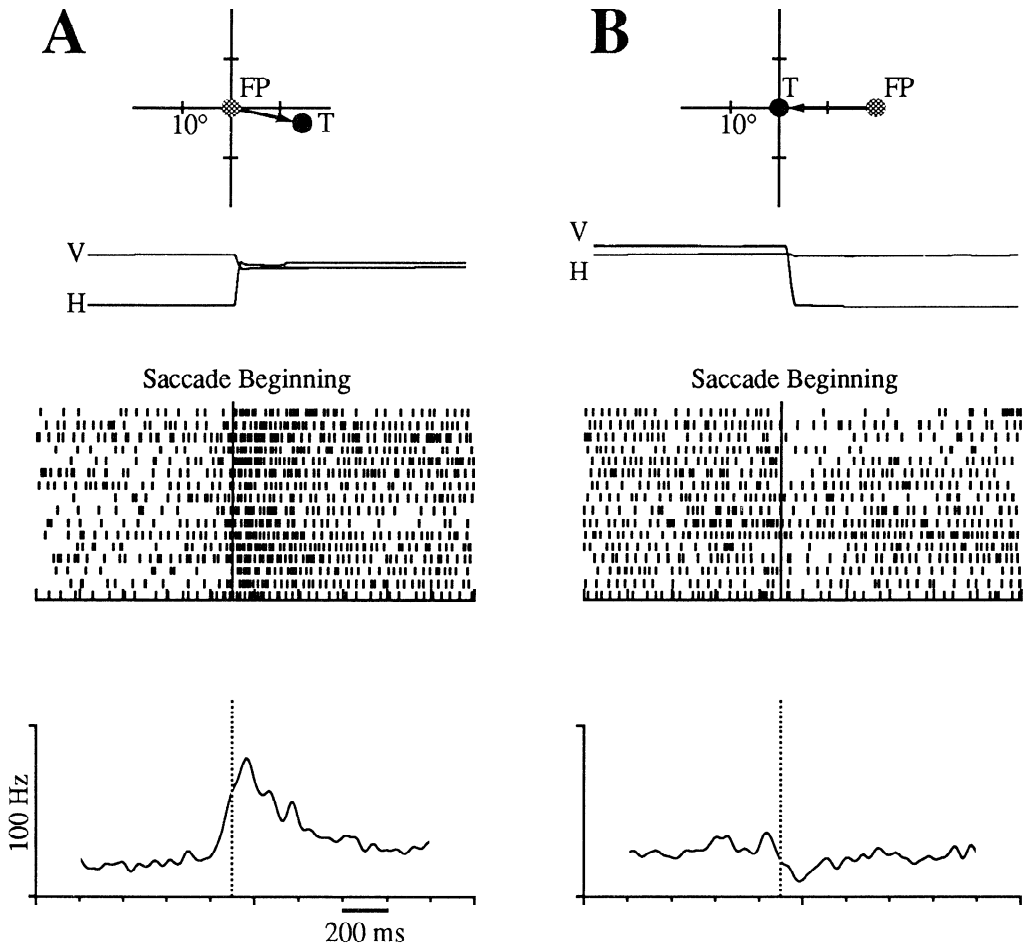

FIG. 10. Activity of corticopontine eye position sensitive neuron during visually guided saccade task. Same neuron as in Fig. 9. In *A*, targets were presented at 15° radius and 342° angle—to the right and slightly down from a fixation point at the center of the tangent screen. In *B*, the monkey's initial fixation point was 20° to the right of the center of the screen, and the target was presented at the center of the screen. For both *A* and *B*, rasters and spike-density profiles are aligned on the beginning of the saccade.

through the omnipause region and began to move ventrolaterally. This activity was similar to that reported by Keller and Crandall and Keller (1985) for the NRTP.

Effects of frontal eye field stimulation on pontine neurons

The frontal eye field was electrically stimulated to assess the effects of its inputs on neurons in the pons. This was done for the right frontal eye field of *monkey MAS01*. Microelectrodes used for stimulation were positioned at cortical sites, where neurons could be antidromically excited from the pons. The effects of right frontal eye field stimulation were examined for neurons in the midline omnipause region and in the left PPRF, dorsolateral to the omnipause region. Test stimuli consisted of one to three pulses delivered with a frequency of 330 Hz; stimulus intensity was ≤1 mA.

EXCITATION OF BURST NEURONS. Frontal eye field stimulation had a very strong effect on burst neurons at locations dorsolateral to the omnipause region (Figs. 13 and 14). As the electrode was advanced through the PPRF, strong excitation was obtained at sites where burst neurons were found. Often, several neuronal spikes were recorded by the pontine electrode in response to a single frontal eye field stimulus. These included spikes from different neurons as well as bursts of spikes from individual neurons. For a sample of eight different burst neuron recording sites, excitation by cortical stimulation with one or two 1-mA pulses

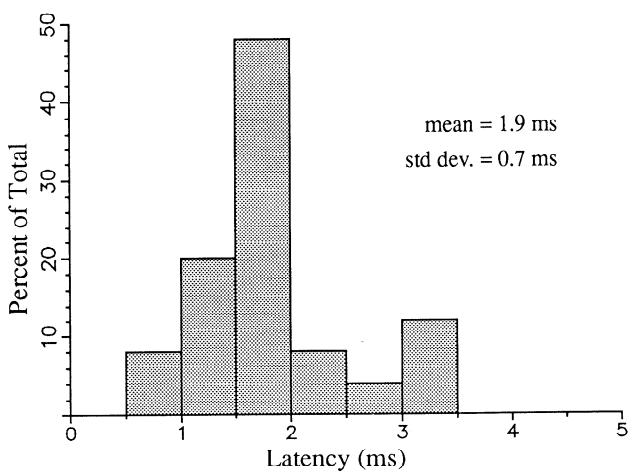

FIG. 11. Latency for antidromic excitation of 25 frontal eye field corticopontine neurons.

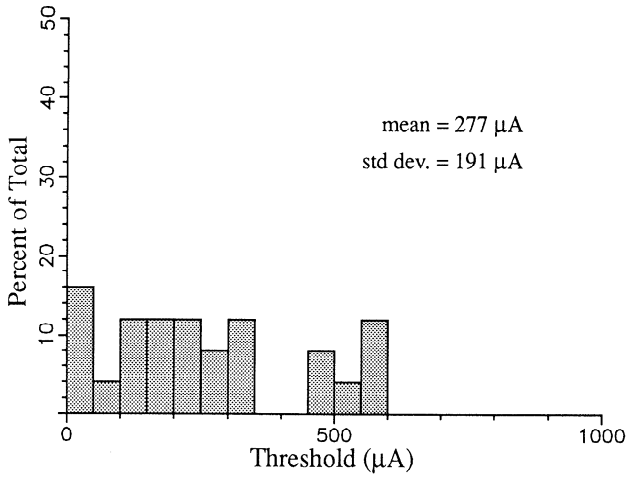

FIG. 12. Threshold for antidromic excitation of 25 frontal eye field corticopontine neurons.

had a minimum latency with a mean of 4.2 ± 0.8 (SD) ms and a maximum latency with a mean of 9.8 ± 3.3 ms. When stimuli included more than one pulse, the latency was always measured from the beginning of the first pulse. The minimum latency for this effect suggests that this excitation of burst neurons by the frontal eye field occurs via a polysynaptic pathway. Figure 13 illustrates the excitation of several neurons by a single frontal eye field pulse. In this example, excitation occurred with latencies between 4.7 and 13.3 ms. Neurons isolated at this site gave bursts in association with leftward saccades (Fig. 14). It should be noted that stimuli consisting of a single 1-mA pulse usually did not evoke an eye movement. Two 1-mA pulses were much more likely to evoke small eye movements, and small eye movements were almost always evoked when three 1-mA pulses were applied at these frontal eye field sites. Burst neurons that could be excited from the frontal eye field began to fire from 70 to 100 ms before the beginning of a saccade. The neuron illustrated in Fig. 14 began to fire ~70 ms before the beginning of the eye movement. These onset times place these cells in the long-lead burst neuron category (Hepp et al. 1989).

Excitation was not seen at sites where burst neurons were not found. Neurons with tonic activity related to eye position encountered in the PPRF, as well as omnipause neurons were not excited by frontal eye field stimulation.

INHIBITION OF OMNIPAUSE NEURONS. Electrical stimulation of the frontal eye field inhibited omnipause neurons, causing them to stop firing. This effect was examined at seven omnipause neuron recording sites. Figure 15 illustrates the effects of a single stimulus train, containing three pulses and lasting a total of 6 ms, on the firing activity of an omnipause neuron. The effect of the cortical stimulus had a very short latency. For most trials, the neuron did not fire after the stimulus began. The latency for the neuron to resume firing, measured from the beginning of the stimulus train, had a mean of 31.7 ± 8.1 ms. This stimulus evoked a small eye movement with mean latency of 23 ms. The eye movement began shortly before the neuron resumed firing. This eye movement was in the appropriate direction, but diminished in amplitude and duration in comparison to eye movements represented by movement neurons at the cortical site, or evoked by conventional electrical stimuli with longer duration and lower current intensity. It is likely that the resumption in the omnipause neuron's activity was responsible for the diminished size and duration of the eye movement. It was not necessary for the cortical stimulus to evoke an eye movement to see an effect on omnipause neurons. Inhibition also occurred in response to stimuli that did not generate eye movements.

The effects of low intensity, longer duration stimuli, typically used for evoking saccades, were examined for comparison with the effects of high-intensity, short-duration stimuli described above (Fig. 16). These stimuli consisted of 70-ms trains of pulses delivered at a frequency of 330 Hz with a maximum intensity of 75 μA. These stimuli also resulted in a cessation of omnipause neuron activity, however, the pause did not begin until ~30 ms after the beginning of the stimulus. The neuron resumed firing when the stimulus stopped. These stimuli always evoked eye movements that occurred during the pause in the neuron's firing. In the example used for Fig. 16, the latency for the evoked eye movement was 36 ms from the beginning of the stimulus. Overall, the mean latency to evoked eye movement with short duration, high-intensity stimuli at eight sites was 18.9 ± 2.5 ms compared with 40.5 ± 10.3 ms for eight sites where long-duration, low-intensity stimuli were administered.

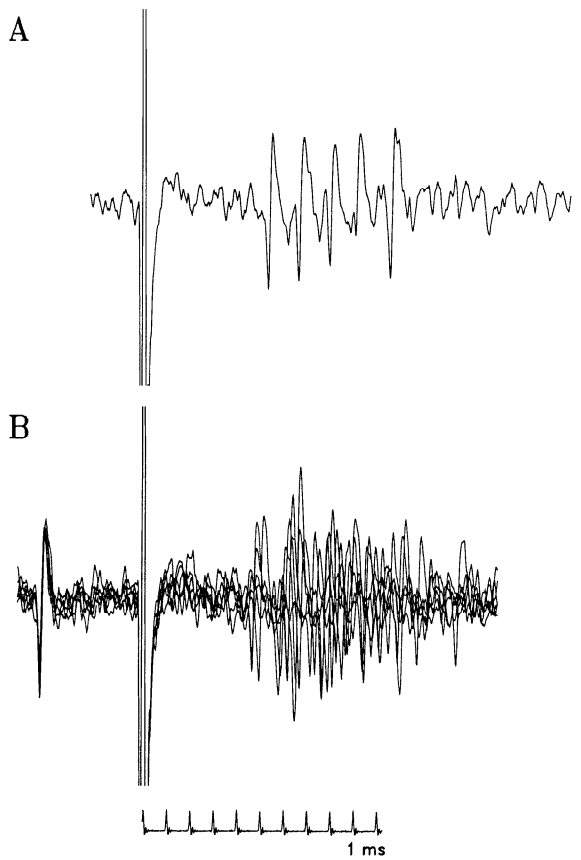

FIG. 13. Excitation of burst neurons in the paramedian pontine reticular formation (PPRF) by frontal eye field stimulation. A single 1-mA biphasic pulse was applied through the frontal eye field electrode. Traces *A* and *B* are aligned on the beginning of the stimulus artifact. *A*: a single trace recorded by the pontine electrode. *B*: superposition of 6 consecutive traces synchronized with the occurrence of the spontaneous firing of the burst neuron whose saccade-related activity is shown in Fig. 14.

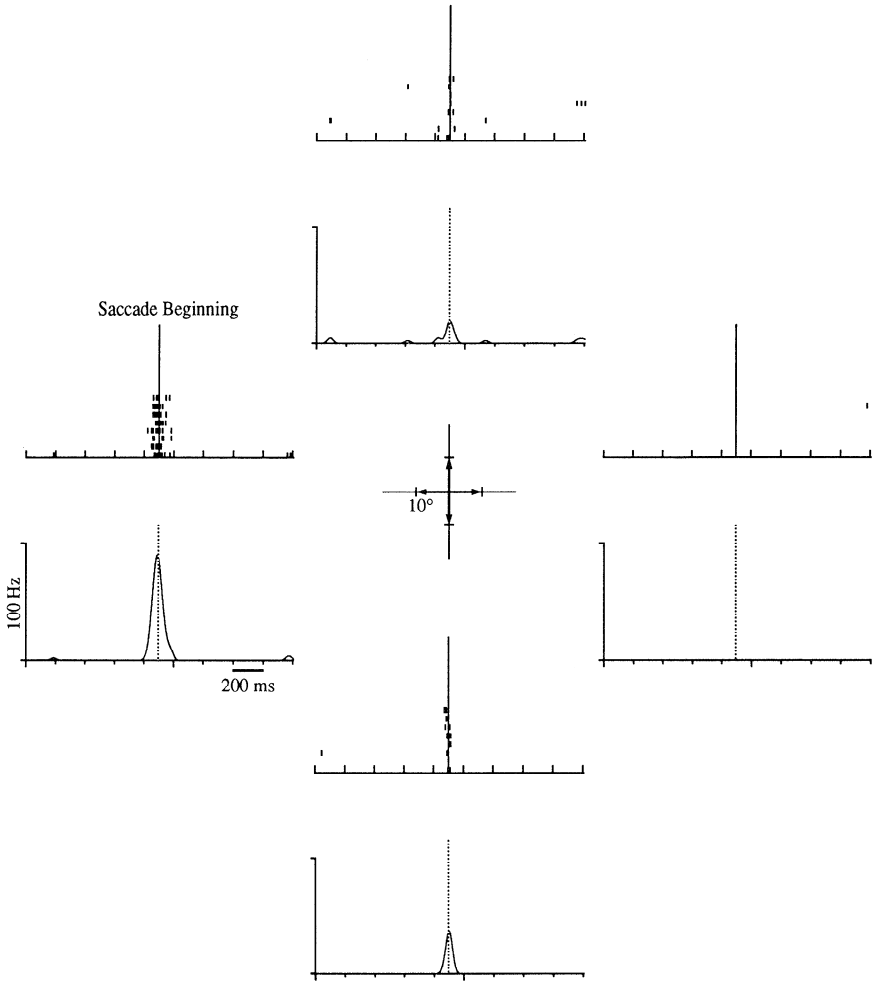

FIG. 14. Activity of a burst neuron in the left PPRF excited by stimulation of the frontal eye field. Activity is shown aligned with the beginning of 10° saccades made in 4 different directions. This is the same neuron as illustrated in Fig. 13.

The duration of the inhibition of omnipause neuron activity was sensitive to the strength of the short-duration cortical stimuli. Figure 17 illustrates the effects of reducing stimulus strength on the duration of time that a omnipause neuron does not fire. The delay between stimulus onset and the next omnipause neuron spike decreases as stimulus intensity is decreased from highs of 31.7 and 28.5 ms at 1 mA, determined from two sets of data collected from the same neuron, to lows of 15.0 and 20.5 ms for a stimulus intensity of 100 μA. The normal mean interval between spikes for this neuron, obtained while the monkey fixated a stationary target, was 13.3 ms, corresponding to a firing frequency of 75 Hz. It should be noted that the method employed to compare the effects of stimulus strength is sensitive only to a complete stop of omnipause neuron activity. It does not indicate when the cortical stimulus might have reduced a pause neuron's firing rate, without stopping it completely.

DISCUSSION

We have demonstrated that rhesus monkey frontal eye field neurons can be antidromically excited by a stimulating microelectrode centered in or near the omnipause region of the pons. The majority of these identified neurons had activity related to saccadic eye movements or activity related to visual stimulation of the fovea and fixation. This activity comprised a subset of the activities of the general population of frontal eye field neurons (Bruce and Goldberg 1985). Prefrontal cortical input to oculomotor regions of the pons could influence neurons a few synapses away from oculomotoneurons. Electrical stimulation of the frontal eye field to assess the effects of these cortical inputs on pontine neurons excited burst neurons, and inhibited omnipause neurons. Both of these effects were exerted with short latency, probably through a short polysynaptic pathway.

Functional activity of frontal eye field neurons projecting to the pons

Several functional classes of frontal eye field neurons were antidromically excited from the omnipause region:

MOVEMENT NEURONS. The largest group of corticopontine neurons were those with activity related to the generation of saccadic eye movements (48%). Movement neurons began to fire ~100 ms before the beginning of a saccade and stopped firing ~100 ms after the end of the eye movement. The peak of their activity coincided with the beginning of the saccade. Most of these neurons had restricted movement fields, they were most active in association with saccades of a specific amplitude and direction. The majority coded eye movements towards the contralateral hemifield.

FOVEAL NEURONS. The second largest group of corticopontine neurons responded to visual stimulation of the fovea

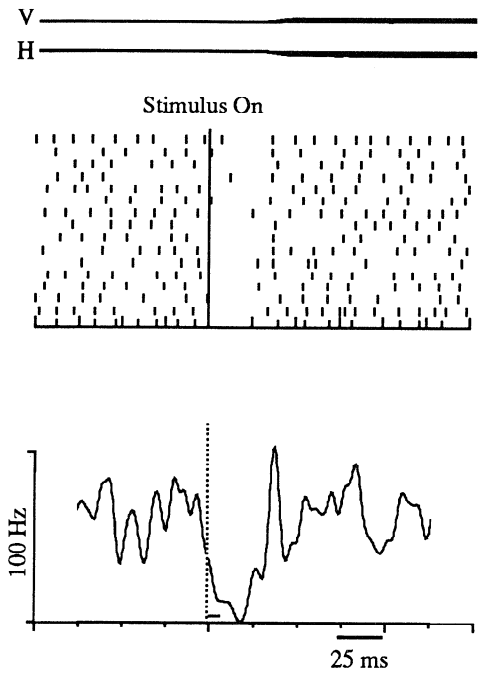

FIG. 15. Inhibition of omnipause neurons by high-intensity short-duration frontal eye field stimuli. Activity of an omnipause neuron during the application of a train of 3 1-mA pulses delivered at a frequency of 330 Hz. The stimulus train lasted 6 ms and is indicated by the short horizontal bar directly above the spike-density profile time-base. Stimuli were applied through the frontal eye field electrode while the monkey fixated a light in the center of the tangent screen. The raster and spike-density profile are aligned on the onset of the electrical stimulation.

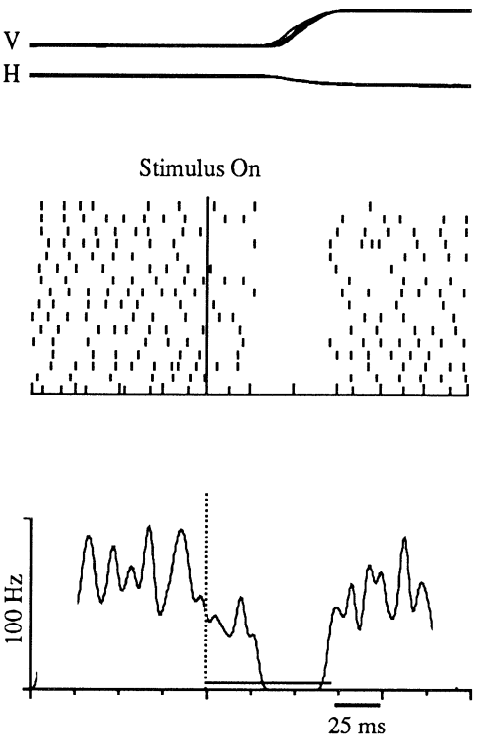

FIG. 16. Inhibition of omnipause neurons by low-intensity long duration frontal eye field stimuli. Activity of same omnipause neuron illustrated in Fig. 15 during the application of a train of 23 75-μA pulses delivered at a frequency of 330 Hz. The stimulus train lasted 70 ms.

and were active in association with visual fixation (28%). All but one corticopontine foveal neuron responded to the onset of a foveal stimulus. The remaining neuron gave an off-response when a foveal stimulus was extinguished. Frontal eye field neurons active during fixation were first described by Bizzi (1968) and later studied by Suzuki and co-workers (1977, 1979). These and other studies suggest that these neurons are not simply visual neurons with receptive fields centered on the fovea but have activity that is related to active fixation and the release of fixation (Bruce and Goldberg 1985; Segraves and Goldberg 1987).

EYE POSITION NEURONS. A small proportion of the population of corticopontine neurons (16%) were sensitive to changes in the direction of gaze.

OTHER NEURONS. Two identified neurons did not fit into the above categories. One neuron was active during smooth pursuit eye movements. Another neuron decreased its activity in association with saccadic eye movements.

Localization of frontal eye field termination sites

Several factors bear on our ability to localize the termination site of neurons antidromically excited in this study. These include the spread of current from the stimulation site, and the anatomic complexity of the region stimulated. At the mean threshold of 277 μA, it is possible that myelinated axons $\leq$1,000 μm away from the tip of the electrode were directly excited by the stimulus. This estimate is based on a review of several studies of stimulation of the mammalian central nervous system (Ranck 1975). The RIP, containing omnipause neurons, is a narrow, midline cell group bordered on either side by rootlets of the abducens nucleus and surrounded by portions of the PPRF containing neurons with oculomotor-related activity (Büttner-Ennever and Büttner 1988; Büttner-Ennever et al. 1988).

When the stimulating electrode was moved up or down in the vicinity of the omnipause region, we found that for 8 of 11 sites tested, the lowest thresholds for antidromically exciting frontal eye field neurons were obtained when the

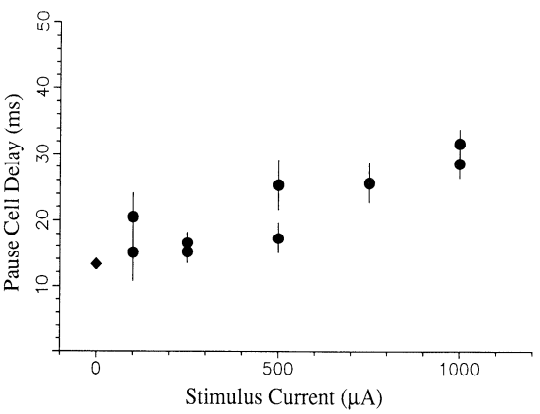

FIG. 17. Comparison of delay to resumption of omnipause neuron activity after frontal eye field stimulation with different current intensities. Stimuli consisted of 3 pulses delivered at a frequency of 330 Hz while the monkey fixated a central light. Current intensities ranged from 100–1,000 μA. Means and standard errors of the mean for 2 sets of data collected from the same neuron are included (●). The diamond at a stimulus intensity of 0 μA indicates the normal delay between spikes for this neuron and indicates a mean of 13.3 ± 0.01 (SE) ms, based on a sample of 2,648 interspike intervals.

tip of the stimulating electrode was within the omnipause region. Thresholds increased dramatically at sites dorsolateral and ventrolateral to the midline omnipause region. The higher threshold sites dorsolateral to the omnipause region include locations where burst neurons were isolated. This result suggests that although antidromic excitation thresholds were sometimes high, the effects of the stimulation was concentrated on axons and terminals located within the omnipause region. In one instance, the minimum threshold site was located <1 mm dorsolateral to omnipause neurons at a site where burst neurons were located. On two occasions, the minimum threshold site was located 1.0–2.5 mm ventrolateral to omnipause neurons, within the basal pontine nuclei or NRTP ipsilateral to the cortical recording site.

In an earlier investigation of corticotectal neurons in the frontal eye field, stimuli to antidromically excite corticotectal neurons were administered at sites separated by >1 mm from nuclei outside of the superior colliculus. This isolation was not possible for the omnipause region. The frontal eye field's projection to the RIP, however, is supplied by the most caudal projections of frontal eye field axons (Huerta et al. 1986; Stanton et al. 1988b), reducing the possibility that axons of passage were stimulated.

Taken together, these results suggest that in all but a few cases our stimulating electrodes excited neurons that terminated in the omnipause region.

Effects of frontal eye field input on pontine neurons

After determining that corticopontine neurons in the frontal eye field were primarily neurons with either movement or foveal/fixation-related activity, we made a preliminary attempt to identify the effects these inputs might have on neurons in the pontine oculomotor centers. This was done by electrically stimulating the frontal eye field while recording from neurons in the pons. This technique was used in the second monkey of this study, after the antidromic excitation experiment was completed. The results obtained from several different stimulation/recording sites were quite similar. Orthodromic stimulation had marked effects on the activity of both burst neurons and omnipause neurons.

BURST NEURONS. Burst neurons are essential to the generation of saccadic eye movements. Their high-frequency burst of activity provides oculomotoneurons with the pulse of activity required to overcome the restraining mechanical forces of the orbit and extraocular muscles and drive the eye to a new location with high velocity (Keller 1974; Luschei and Fuchs 1972). See (Hepp et al. 1989) for review. When the recording electrode was positioned dorsolateral to the omnipause region in the PPRF, stimulation of the frontal eye field had strong excitatory effects on burst neurons. Often several burst neurons were excited at a single recording site. The minimum and maximum latency for this effect ranged from means of 4.2–9.8 ms, suggesting that one or more synaptic relays was positioned between the cortical neuron and pontine burst neuron. This agrees with the anatomic findings that direct inputs from the frontal eye field to the PPRF are relatively sparse (Huerta et al. 1986; Leichnetz et al. 1984; Stanton et al. 1988b). In lieu of direct cortical projections, a likely source of input to these neurons is from the superior colliculus, where stimulation has been shown to directly excite burst neurons (Raybourn and Keller 1977). We estimated the number of synaptic relays between the frontal eye field and the pontine neuron with methods similar to those of Raybourn and Keller (1977). Given our antidromic conduction latencies from pons to frontal eye field of 0.8–3.4 ms, and assuming a synaptic delay of 0.5 ms and a rise time of 0.1 ms for the extracellularly recorded action potential, the range of times for monosynaptic excitation of the pontine neuron would be 1.4–4.0 ms. For a disynaptic pathway with a synapse in the superior colliculus and estimated conduction time from the superior colliculus to the pons of 0.3 ms, latencies could be expected to range from 2.3 to 4.9 ms. Thus all of the measured conduction times were likely to result from polysynaptic pathways and could have included synapses in the superior colliculus as well as within the pons. All of the burst neurons that we were able to excite from the frontal eye field began to fire 70–100 ms before the beginning of the saccade. Their onset-time was long before the time for pause neurons to turn off at ~15 ms before the beginning of the saccade. Thus these neurons should be characterized as long-lead burst neurons. Long-lead burst neurons are believed to provide movement related input to short-lead burst neurons that are tonically inhibited by omnipause neurons and do not begin to fire until ≤15 ms before the beginning of the saccade (Hepp et al. 1989; Scudder 1988; Van Gisbergen and Van Opstal 1989). It is known that the superior colliculus excites long-lead but not short-lead burst neurons (Raybourn and Keller 1977).

OMNIPAUSE NEURONS. Omnipause neurons provide the trigger to generate a saccade. Their high tonic firing inhibits burst neurons. Pause neurons stop firing when it is time to begin a saccade. This allows burst neurons to fire, exciting oculomotoneurons, and 10–15 ms later the saccade begins. Electrical stimulation of the frontal eye field inhibited omnipause neurons. The time that the neuron remained silent was proportional to the strength of the stimulus. It was not necessary for the cortical stimulus to evoke an eye movement for this inhibition to occur. Inhibition appeared to begin immediately after the start of the stimulation, although it is much more difficult to determine a precise latency when observing inhibition. For an omnipause neuron firing with a frequency of 100 Hz, its interspike interval of 10 ms results in a 10-ms period over which the neuron might fire after the beginning of the cortical stimulus. With a 1-mA pulse train of 6-ms duration, a resumption in firing was not observed until an average of 23 ms after the beginning of the stimulus train. Although the inhibition appeared to occur with very short latency, we do not take this as evidence for direct inhibition of omnipause neurons by frontal eye field neurons. We are unaware of evidence for inhibitory corticofugal projections. On the contrary, an excitatory role for frontal eye field corticopontine neurons is supported by the finding that the distribution of the inhibitory neurotransmitter GABA is very sparse within layer V of the frontal eye field where the corticopontine neurons are located (Schwartz et al. 1985). GABA appears to be contained within stellate-shaped interneurons in prefrontal

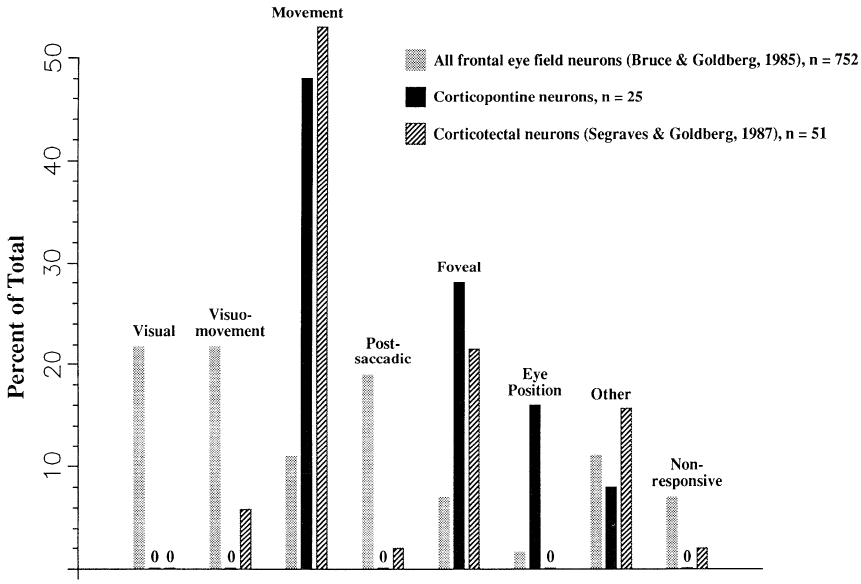

FIG. 18. Distribution of activity types for the general population of frontal eye field neurons, corticopontine neurons, and corticotectal neurons.

cortex and is not found in the layer V pyramidal neurons that give rise to the corticofugal projection (Schwartz et al. 1988). It is likely that the frontal eye field input excites an inhibitory interneuron adjacent to pause cells which, in turn, inhibits the pause cells.

The effects of frontal eye field stimulation on omnipause and burst neurons are in many ways similar to those demonstrated by Raybourn and Keller (1977) for superior colliculus inputs to these same neuron types. One exception is that collicular stimulation produced an initial excitation of omnipause neurons followed by inhibition. Frontal eye field stimulation did not excite omnipause neurons. Raybourn and Keller (1977) proposed that omnipause neurons were turned off by long-lead burst neurons that were directly excited by the superior colliculus. The strong projection of the frontal eye field to the superior colliculus could turn off omnipause neurons via this pathway. Our present study suggest a parallel pathway whereby the frontal eye field's direct projection to the RIP turns off omnipause neurons via local inhibitory interneurons.

Comparison of the corticopontine, corticotectal, and general populations of frontal eye field neurons

Figure 18 compares the distribution of activity types for frontal eye field neurons antidromically excited from the pons to published distributions of activity types for the entire population of frontal eye field neurons (Bruce and Goldberg 1985) and for corticotectal neurons identified by antidromic excitation from the superior colliculus (Segraves and Goldberg 1987). Most notably, the proportions of movement and foveal neurons in the population of corticopontine neurons is greatly enhanced in comparison with the proportions of these neuron types in the general population. Forty-eight percent of identified corticopontine neurons had movement activity versus 11% of all frontal eye field neurons. Twenty-eight percent of corticopontine neurons had foveal activity versus 7% of the entire population. Despite quantities within the general population near 20%, there were no neurons antidromically excited from the pons with visual, visuomovement, or postsaccadic activity.

The distributions of activity types for corticopontine and corticotectal neurons are quite similar. For both groups with corticofugal projections, the percentage of movement and foveal neurons is enriched compared with the general population. Moreover, they both include few or no neurons with visual, visuomovement, or postsaccadic activity. Thus similar information is sent by the frontal eye field to the superior colliculus and pons.

Are corticopontine and corticotectal fibers collaterals of the same axon?

Given the similarity between the activity types of corticopontine and corticotectal neurons, one must consider the possibility that these projections arise from the same neurons, which branch at some point to send collaterals to both targets. Most axons of the frontal eye field projecting to the superior colliculus and omnipause region arise from the same transthalamic pathway (Huerta et al. 1986; Leichnetz 1981; Stanton et al. 1988b). This pathway splits within the posterior thalamus, giving rise to fascicles directed towards the superior colliculus and RIP. Branching axons are not uncommon for corticopontine neurons (Giolli and Towns, 1980), and cortical neurons that send branches to both the colliculi and the pons have been identified in the cat (Keizer et al. 1987). It is entirely possible that individual movement and foveal neurons in the frontal eye field terminate at both tectal and pontine sites. We have not attempted to address this question experimentally and feel that the presence or absence of bifurcating axons would neither add nor subtract from the finding that the information sent from frontal eye field to superior colliculus and omnipause regions is quite similar.

Eye position neurons

Four corticopontine neurons, 16% of the population, had tonic firing activity that was modulated by the position of the eye in the orbit. This neuron type was rare in the general population, 1.6% or 12 of 752 neurons (Bruce and Goldberg 1985). Neurons with activity related to eye position

were not found in the corticotectal population. These neurons showed phasic increases or decreases in activity surrounding eye movements towards or away from their preferred eye position. Their tonic activity reflected current, not future, eye position. Although eye position neurons were found in only one of the two monkeys used in this study, they were not isolated to a single location in that monkey but were distributed among four separate recording sites and were antidromically excited from three different pontine stimulation sites. Because of the relatively small number of antidromically excited neurons that are successfully isolated and functionally characterized in these experiments, we can not rule out the possibility that eye position neurons were missed in the corticotectal experiment (Segraves and Goldberg 1987). Another possibility, however, is that these neurons represent a distinct difference between the frontal eye field's corticopontine and corticotectal projections. A recent model of the superior colliculus proposes that much of the processing within the intermediate layers of the superior colliculus is concerned with desired eye displacement and outputs a spatially coded motor error signal to pontine oculomotor centers (Waitzman et al. 1991). This processing would not require the knowledge of absolute eye position. It is unclear, however, why the frontal eye field would send an eye position signal to the pons. Although eye position information is important at levels close to oculomotoneurons, many pontine neurons already carry this signal and would not need to obtain it via cortical input.

Frontal eye field contributions to the generation of eye movements

The present study, in combination with our previous characterization of frontal eye field corticotectal projections (Segraves and Goldberg 1987) increases our understanding of how the frontal eye field contributes to the generation of saccadic eye movements. At present, it is appreciated that several regions of cerebral cortex are involved in the generation of voluntary saccades, including posterior parietal cortex, as well as the frontal and supplementary eye fields in prefrontal cortex. From among this group, the frontal eye field appears to be most closely associated with the motor aspects of generating saccades, whereas activity in parietal cortex and supplementary eye field is associated with the sensory, integrative, and planning aspects of saccade generation (Andersen and Gnadt 1989; Goldberg and Segraves 1989; Schall 1991). Figure 19 diagrams the frontal eye field's inputs to brain stem oculomotor centers. The connections between the superior colliculus, omnipause neurons, and long and short-lead burst neurons reflect our current understanding of these pathways (for reviews, see Hepp et al. 1989, Scudder 1988, and Van Gisbergen and Van Opstal 1989). We have found that movement and foveal neurons in the frontal eye field send a signal to the superior colliculus and to the vicinity of omnipause neurons that conveys the amplitude and direction of an intended saccade (where) and the trigger to initiate the saccade (when). The frontal eye field has a second powerful input to the superior colliculus by way of the caudate nucleus and substantia nigra (Hikosaka and Wurtz 1983). We

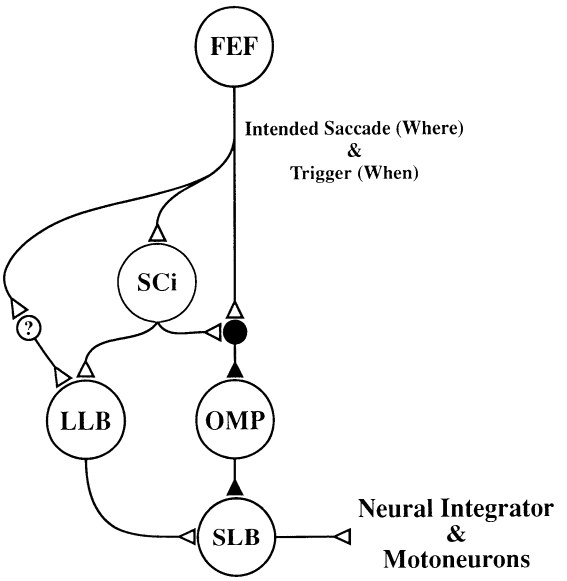

FIG. 19. Frontal eye field inputs to brain stem oculomotor centers. Filled synapses are inhibitory. FEF, frontal eye field; LLB, long-lead burst neurons; OMP, omnipause neurons; SCi, intermediate layers of superior colliculus; SLB, short-lead burst neurons.

expect that the frontal eye field to superior colliculus pathway via the basal ganglia would have the powerful effect of turning off the substantia nigra's inhibition of the superior colliculus at the same time that direct projections from the cortex are exciting the superior colliculus. Signals carried by the frontal eye field to the caudate nucleus, however, have not been identified. For simplicity, the basal ganglia pathway has been omitted from Fig. 19. The present findings concerning electrical stimulation of the frontal eye field have shown that frontal eye field inputs excite burst neurons and inhibit omnipause neurons within several milliseconds of their initiation. Neither of these effects are believed to be direct and are likely to involve one or more interneurons. As Fig. 19 suggests, we believe that frontal eye field axons projecting to the omnipause region excite neurons, which then inhibit omnipause neurons, causing them to stop firing. The trigger signal could come from foveal or movement neurons, or both. The intended saccade signal is carried to the superior colliculus where it may be used to help generate a collicular signal that is sent to the long-lead burst neurons. There are conflicting reports concerning the nature of the collicular output signal, however, several possibilities include static or dynamic motor error and eye velocity (Berthoz et al. 1986; Keller 1979; Munoz et al. 1991; Scudder 1988; Sparks and Mays 1980; Waitzman et al. 1991). The saccadic system must also be able to make use of frontal eye field movement activity sent directly to the PPRF. Primary support for the efficacy of this pathway is provided by the finding that removal of the superior colliculus does not abolish a monkey's ability to make visually guided saccades (Schiller et al. 1980), although removal of both superior colliculus and frontal eye field has a devastating effect on the ability to generate saccades. In the absence of a superior colliculus, the frontal eye field must access the brain stem oculomotor system via its direct projections to the pons. In addition, a recent report suggests that the frontal eye field can alter the trajectory of a saccade via a path-

way that bypasses the superior colliculus and presumably goes directly to the pons (Schlag-Rey et al. 1992). Because the activation of burst neurons by frontal eye field stimulation occurred at latencies of ≥4 ms, we presume that this pathway includes at least one neuron interposed between the frontal eye field and burst neurons. The identity of these additional neurons is unknown.

Timing of frontal eye field input to superior colliculus and pons

The latency and spike activity for foveal and movement neurons are consistent with their providing intended saccade and trigger signals to the brain stem. Foveal neurons respond with latencies of ~50–100 ms to the appearance or disappearance of the fixation light. Their activity can be modulated by blinking the fixation light off and on during a fixation task. This modulation is consistent with their proposed role in saccade initiation, because saccades are generated with significantly shorter latency when the fixation point is turned off 150–250 ms before a peripheral target appears (Fischer and Boch 1983). In this situation, it is likely that foveal neurons have removed their inhibitory influence on the saccade generator before the target appears. Movement neurons in the frontal eye field begin to increase their activity 100–300 ms before the start of a saccade. Their activity peaks at the start of the saccade and goes back to resting level ~100–200 ms after the end of the saccade (Segraves et al. 1990). This type of activity profile is consistent with movement neurons providing an intended saccade signal as well as the trigger to allow the eye movement to proceed.

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