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# Frontal Eye Field Sends Delay Activity Related to Movement, Memory, and Vision to the Superior Colliculus

MARC A. SOMMER AND ROBERT H. WURTZ

Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland 20892-4435

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**Sommer, Marc A. and Robert H. Wurtz.** Frontal eye field sends delay activity related to movement, memory, and vision to the superior colliculus. *J Neurophysiol* 85: 1673–1685, 2001. Many neurons within prefrontal cortex exhibit a tonic discharge between visual stimulation and motor response. This *delay activity* may contribute to movement, memory, and vision. We studied delay activity sent from the frontal eye field (FEF) in prefrontal cortex to the superior colliculus (SC). We evaluated whether this efferent delay activity was related to movement, memory, or vision, to establish its possible functions. Using antidromic stimulation, we identified 66 FEF neurons projecting to the SC and we recorded from them while monkeys performed a Go/Nogo task. Early in every trial, a monkey was instructed as to whether it would have to make a saccade (Go) or not (Nogo) to a target location, which permitted identification of delay activity related to movement. In half of the trials (memory trials), the target disappeared, which permitted identification of delay activity related to memory. In the remaining trials (visual trials), the target remained visible, which permitted identification of delay activity related to vision. We found that 77% (51/66) of the FEF output neurons had delay activity. In 53% (27/51) of these neurons, delay activity was modulated by Go/Nogo instructions. The modulation preceded saccades made into only part of the visual field, indicating that the modulation was movement-related. In some neurons, delay activity was modulated by Go/Nogo instructions in *both* memory and visual trials and seemed to represent where to move in general. In other neurons, delay activity was modulated by Go/Nogo instructions only in memory trials, which suggested that it was a correlate of working memory, or only in visual trials, which suggested that it was a correlate of visual attention. In 47% (24/51) of FEF output neurons, delay activity was unaffected by Go/Nogo instructions, which indicated that the activity was related to the visual stimulus. In some of these neurons, delay activity occurred in both memory and visual trials and seemed to represent a coordinate in visual space. In others, delay activity occurred only in memory trials and seemed to represent transient visual memory. In the remainder, delay activity occurred only in visual trials and seemed to be a tonic visual response. In conclusion, the FEF sends diverse delay activity signals related to movement, memory, and vision to the SC, where the signals may be used for saccade generation. Downstream transmission of various delay activity signals may be an important, general way in which the prefrontal cortex contributes to the control of movement.

## INTRODUCTION

The primate frontal eye field (FEF) in the posterior prefrontal cortex contributes to the generation of saccadic eye move-

ments (reviewed by Schall 1997 and Tehovnik et al. 2000); neurons in the FEF carry diverse signals ranging from visual responses to saccade-related bursts of activity (e.g., Bruce and Goldberg 1985). A major projection of FEF neurons is to the superior colliculus (SC) (reviewed by Leichnetz and Goldberg 1988), a midbrain structure that, compared with the FEF, is more intimately linked to the brain stem saccade-generating circuitry (Büttner-Ennever and Büttner 1988; Chen and May 2000; Segraves and Park 1993). Evidence that the projection from FEF to SC plays an important role in saccade generation has accumulated. Activity in the FEF modulates SC neuronal discharges (Schlag-Rey et al. 1992) and the ability to evoke saccades electrically from the FEF can be blocked by SC inactivation (Hanes and Wurtz 2001). By antidromically activating FEF neurons using a pulse of electrical stimulation in the SC, we and others identified FEF output neurons and showed that they send a multitude of signals, from visual-related to saccade-related, to the SC (Everling and Munoz 2000; Segraves and Goldberg 1987; Sommer and Wurtz 2000).

We previously showed that a prevalent signal sent from the FEF to the SC is *delay activity* that intervenes between the sensory stimulus and the motor response (Sommer and Wurtz 2000). Delay activity in the FEF and in other prefrontal regions may contribute to a variety of functions, including motor planning, working memory, and visual perception, as is suggested by lesion and recording studies. Ablation or reversible inactivation of the FEF or other prefrontal regions profoundly disrupts movements made toward remembered stimuli and also can impair visual perception, visual attention, and movements made toward visual stimuli (e.g., Deng et al. 1986; Dias and Segraves 1999; Funahashi et al. 1993a; Jacobsen 1935, 1936; Latt 1977; Latt and Cowey 1971; Sommer and Tehovnik 1997; for reviews see Fuster 1997 and Tehovnik et al. 2000). Consistent with the idea that prefrontal delay activity contributes to a variety of functions, recording studies in the FEF and other prefrontal regions have shown that in some neurons the delay activity is related to movement whereas in others it is related to visual stimulation; the latter, stimulus-related delay activity can be mnemonic in nature, occurring if the stimulus has to be remembered, or more visual in nature, occurring only when a stimulus remains visible (e.g., Bruce and Goldberg 1985; Funahashi et al. 1993b; Niki and Watanabe 1976; Watanabe 1986a,b). In our previous study of FEF neurons that

Address for reprint requests: M. A. Sommer, Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Building 49, Room 2A50, 9000 Rockville Pike, Bethesda, MD 20892-4435 (E-mail: mas@lsr.nei.nih.gov).

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project to the SC, we detected delay activity by using a task in which a target appeared and then a delayed saccade *always* was made toward it (Sommer and Wurtz 2000). This task did not permit us to distinguish activity related to the stimulus from that related to the movement, which limited our ability to interpret the functions of the delay activity.

In the present study our goal was to characterize in detail the delay activity sent from the FEF to the SC. We identified FEF neurons that projected to the SC (Fig. 1, *A* and *B*) and recorded from them while monkeys performed a delayed Go/Nogo task (Fig. 1, *C* and *D*). The key feature of this task was that a target always appeared but a monkey did *not* always make a saccade to it. Prior to the delay period in every trial, a monkey was instructed as to whether it would have to make a saccade (Go

or not (Nogo) to the target location. If delay activity differed in Go versus Nogo trials, then it was related to movement. To characterize this activity in more detail, we examined whether it was related to making a specific range of saccadic vectors, whether its intensity predicted reaction time, and whether the activity always predicted saccade generation, even in error trials. Delay activity that did *not* differ in Go versus Nogo trials was unrelated to movement; instead, it likely was related to the visual stimulus. To permit further characterization of this delay activity, in half of the trials the target disappeared so that it had to be remembered during the delay period and in the other trials the target remained lit. This allowed us to distinguish delay activity related to remembering a visual stimulus from delay activity that was a simple tonic visual response.

We found that the FEF sends to the SC a wide assortment of delay activity signals that are related in various ways to movement, memory, and vision. This suggests that the delay activity sent from the FEF to the SC contributes to several different functions during saccade generation. Moreover, these results provide the first detailed description of delay activity identified as leaving *any* part of the prefrontal cortex. We hypothesize that a major, general way in which prefrontal cortex influences behavior is to send a diversity of delay activity signals to more motor-related regions.

An abstract of this work appeared previously (Wurtz and Sommer 1998).

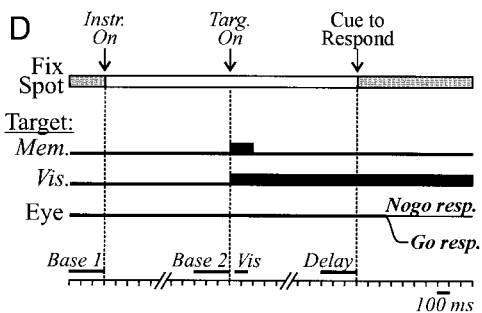
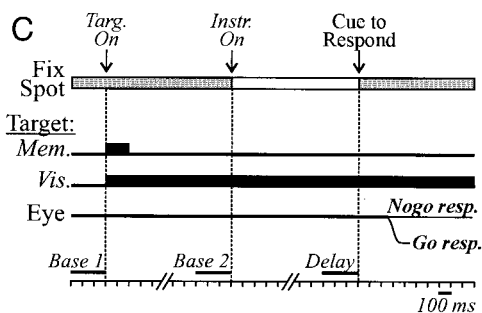
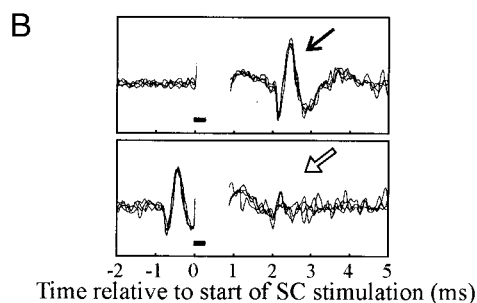
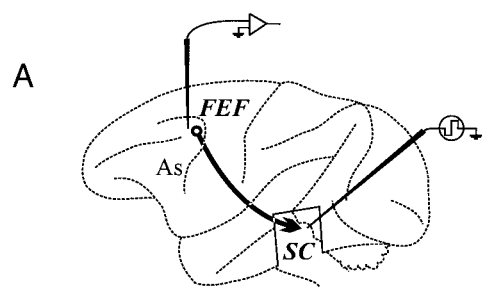


FIG. 1. Summary of methods. *A*: lateral view of the rhesus monkey brain. We recorded exclusively from frontal eye field (FEF) neurons that projected to the superior colliculus (SC) (shown in cutaway view). Projection of an FEF neuron was identified by showing that it was antidromically activated by electrical stimulation in the SC. As, arcuate sulcus. *B*: examples of action potential waveforms showing application of the collision test. FEF recording waveforms from four consecutive trials of stimulating the SC at time 0 are superimposed in each of the *top* and *bottom* illustrations. *Top*: the FEF neuron fired reliably (black arrow) about 2 ms after a stimulation pulse was applied to the SC (pulse duration indicated by black bar). Stimulation artifact is erased for clarity. *Bottom*: when the SC stimulation was timed to occur just after the FEF neuron fired spontaneously, stimulation always failed to evoke an action potential from the FEF neuron (white arrow). The failure occurred because the stimulation-evoked action potential traveling toward the soma of the neuron was annihilated by the spontaneous action potential traveling away from the soma along the same axon. Failure of the stimulation-induced spike only happened if stimulation began  $< 2.4$  ms after the onset of the spontaneous spike. The neuron therefore passed the collision test, which indicated that it was antidromically activated from the SC. *C* and *D*: timing diagrams of the delayed Go/Nogo task. In all trials, the monkey first foveated a spot (Fix Spot) initially colored blue. Then the two main task events occurred: presentation of the peripheral target (Targ. On) and presentation of the foveal instruction onset (Instr. On). *C*: target-first trials, in which target onset preceded instruction onset. A target appeared and then, after a randomized delay period, the Fix Spot changed to green for Go or red for Nogo trials. The instruction period is illustrated in white in the Fix Spot bar. *D*: instruction-first trials, in which the order of task events was reversed. The instruction was presented first and, after a randomized delay period, the target appeared. In all trials (*C* and *D*), a second randomized delay period ensued and then the Fix Spot changed back to blue (depicted as transition from white to gray in Fix Spot bar), which was the cue to respond. At this point, the monkey was required to make its response, which was a saccade to the target in Go trials (Go resp., Eye trace) or continued fixation in Nogo trials (Nogo resp., Eye trace). Targets were flashed for 200 ms in memory trials (Mem.) or were persistently lit in visual trials (Vis.). *C* and *D*, *bottom*: the time scale (100 ms/division) and analysis epochs are illustrated (Base 1, first baseline epoch; Base 2, second baseline epochs; Vis, visual response epoch; Delay, delay epoch).

## METHODS

## Physiology

The present data were collected from the same neurons studied with other tasks in a prior report and physiological methods are described in detail there (Sommer and Wurtz 2000). Briefly, two monkeys (*Macaca mulatta*) were implanted with recording cylinders for accessing the brain, scleral search coils for recording eye position, a plug for accessing eye coil leads, and a post for immobilizing the head during recording sessions. All procedures were approved by the Institute for Animal Care and Use Committee and complied with Public Health Service policy on the humane care and use of laboratory animals. We found the FEF and the SC by using recording and stimulation criteria (e.g., by locating sites at which stimulation-evoked saccades were evoked with a  $<50 \mu\text{A}$  threshold) and confirmed the localizations with magnetic resonance imaging. We recorded single neurons extracellularly in the FEF and showed that they projected to the SC by antidromically activating them with an electrical stimulation pulse applied to the SC intermediate layer through a chronically implanted microelectrode (Fig. 1A). We verified antidromic activation of every neuron using the collision test (Fig. 1B).

## Behavior

We recorded neuronal activity while a monkey performed a delayed Go/Nogo task (Fig. 1, C and D). The main purpose of this task was to vary the requirement to make a saccade so that we could see if delay activity was related to movement. In all trials, a monkey first foveated a blue spot at the center of a tangent screen for 500–800 ms (all timings were pseudorandomized on a trial-by-trial basis). In half of the trials (Fig. 1C), a peripheral visual target then appeared, followed 800–1200 ms later by the instruction. In the other half of the trials (Fig. 1D), the order was reversed so that the instruction appeared first. The instruction took the form of a color change of the foveated spot from blue either to green (Go instruction) or red (Nogo instruction). In all trials, after both target and instruction appeared, a second delay period of 800–1200 ms ensued. The foveated spot then changed from its instruction color back to its initial color (blue) as a cue to respond. In Go instruction trials, we rewarded the monkey if it made a *Go response*, which is defined as a saccade to the target initiated 60–500 ms after the cue to respond. In Nogo instruction trials, we rewarded the monkey if it made a *Nogo response*, which is defined as steady fixation of the central spot for 1000 ms after the cue to respond. Unless otherwise noted, targets always appeared at the center of the neuron's visual and/or movement field as mapped prior to running the task (see Sommer and Wurtz 2000). We randomized target-first (Fig. 1C) and instruction-first (Fig. 1D) trials because we wanted the first event in each trial to be unpredictable, to minimize the possibility that neurons might exhibit anticipatory activity during the initial fixation period (anticipatory activity is common in the FEF; Bruce and Goldberg 1985). This was important because activity in the initial fixation period served as a reference for detecting delay period discharges later in the trial (see *Analysis*).

For delay activity that was unaffected by Go/Nogo instructions, which suggested that it was related to the visual stimulus rather than to the motor response, we wanted to be able to analyze whether the activity was related to memory of the stimulus or whether it was simply a tonic visual response. Therefore, in half of the trials (memory trials) the target appeared for only 200 ms so that its location had to be remembered (*Mem.* in Fig. 1, C and D) and in the remaining trials (visual trials) the target appeared and remained until the end of the trial (*Vis.* in Fig. 1, C and D). In summary (see Table 1), there were eight different, randomly interleaved trial types: Go and Nogo memory trials (Table 1, top row), Go and Nogo visual trials (Table 1, bottom row), and target-first and instruction-first versions of each.

TABLE 1. *Randomly interleaved trial types*

	Movement Instruction	
	Go	Nogo
Target:		
Memory	Go memory	Nogo memory
Visual	Go visual	Nogo visual

For each of the four trial types shown, either the target or the instruction could appear first (see Fig. 1, C and D), which yields an overall total of eight randomly interleaved trial types.

We began recording after monkeys had been trained for several weeks and had reached stable levels of performance. During recording sessions, 98.5% of trials were correct (Go responses in Go trials or Nogo responses in Nogo trials) and 1.5% were incorrect (Nogo responses in Go trials or Go responses in Nogo trials). Only correct trials were analyzed except where otherwise noted in RESULTS. We discarded trials ending in responses that did not meet our definition of a Go or Nogo response.

For details regarding visual stimulation and data collection, see Sommer and Wurtz (2000). Briefly, foveal and peripheral stimuli were  $0.3 \times 0.3^\circ$  squares of light back-projected onto a tangent screen by a liquid crystal display projector. Single neuron data, task event data, and eye position samples were collected at 1 kHz using a personal computer real-time acquisition system. Colors were not adjusted to isoluminance and therefore may have differed in luminance as well as in chrominance.

## Analysis

Saccades were automatically detected in the recorded eye position traces using a computer program that ran a template matching algorithm; accuracy of the saccade detection was verified by visual inspection of data from every trial. Saccadic reaction time was defined as the time from the cue to respond to the initiation of the saccade. A saccade was judged to be spatially accurate if it terminated within a virtual window surrounding the target location, the dimensions of which varied from  $1^\circ$  horizontally and  $2^\circ$  vertically for targets located at small eccentricity (e.g.,  $4^\circ$  from the fovea), up to  $10 \times 20^\circ$  for targets located at large eccentricity (e.g.,  $40^\circ$  from the fovea).

To analyze the activity of a neuron, we calculated the neuron's mean firing rates during various epochs of the task. We primarily analyzed delay activity measured 300–0 ms before the cue to respond (Delay epoch in Fig. 1, C and D), but in one section of the RESULTS we also analyzed short-latency visual responses during instruction-first trials measured 50–150 ms after target onset (Vis epoch in Fig. 1D). For comparison with activity levels during the Delay and Vis epochs, we measured reference levels of activity during two baseline epochs called Base 1 and Base 2. In target-first trials (Fig. 1C), the Base 1 epoch was 300–0 ms before target onset and the Base 2 epoch was 300–0 ms before instruction onset. In instruction-first trials (Fig. 1D), the Base 1 epoch was 300–0 ms before instruction onset and the Base 2 epoch was 300–0 ms before target onset. We calculated mean firing rates by finding the average number of spikes occurring in an epoch and dividing this value by the epoch duration.

A significance level of  $P < 0.05$  was used for statistical tests. We compared mean firing rates between epochs with Student's *t*-test or the Mann-Whitney rank sum test, using the former if the data were normal (determined with the Kolmogorov-Smirnov test) and of equal variance (determined with the Levene Median test) and the latter otherwise. The mean firing rate in an epoch could be used in up to three comparisons so, to be conservative, we uniformly adjusted the significance level to  $P < 0.0167$  ( $=0.05/3$ , Bonferroni correction) for all comparisons of firing rates between epochs.



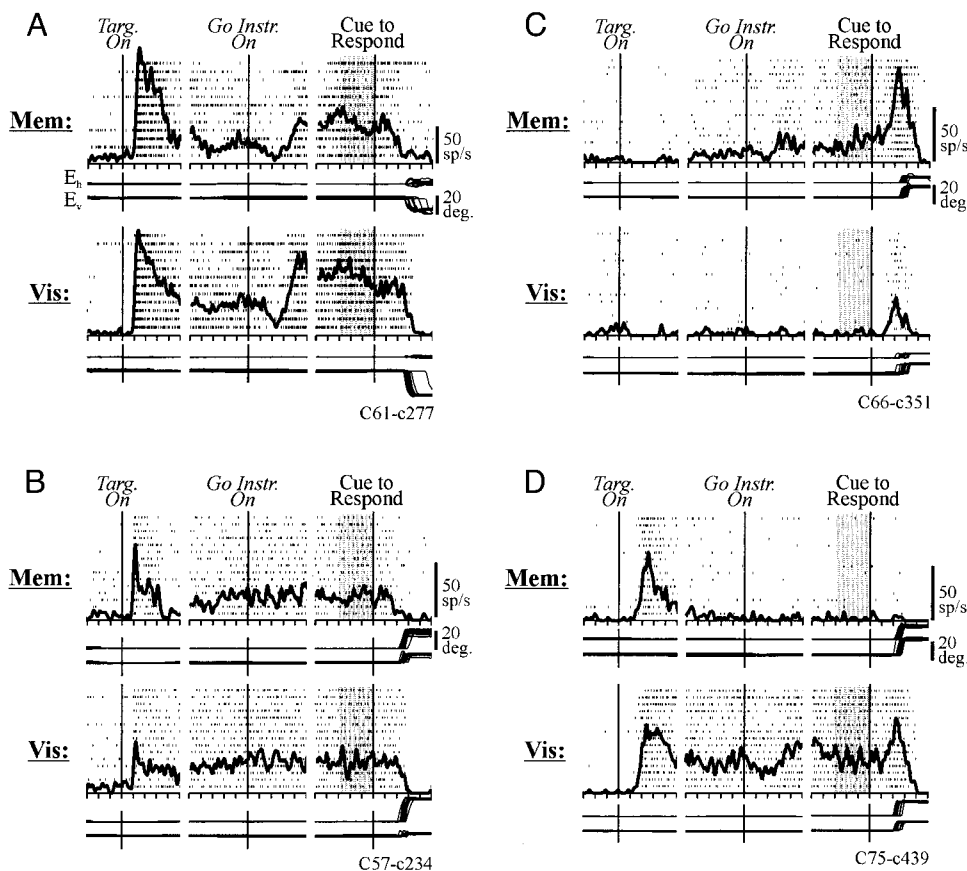


FIG. 2. Delay activity in four example neurons. *A–D*: data from memory trials are shown above (Mem.) and data from visual trials are shown below (Vis.). For illustration, only target-first, Go-instructed trials are shown; data are aligned to target onset (Targ. On), to onset of the Go instruction (Go Instr. On), and to the cue to respond. Rows of tick marks represent action potentials recorded in individual trials. Spike density functions show average firing rates [constructed by replacing the spikes with Gaussians (width,  $\sigma = 10$  ms) and summing them; MacPherson and Aldridge 1979]. Delay activity is highlighted with shaded boxes. Below the rasters and spike density functions are ticks in 100 ms intervals and eye position decomposed into horizontal ( $E_h$ ) and vertical ( $E_v$ ) traces (upward deflections in the eye traces represent rightward movements for  $E_h$  and upward movements for  $E_v$ ). Scale bars for spike density functions and eye position traces are to the right of each panel. Sp, spikes; deg., degrees. Code for identifying each neuron is at bottom right of each panel. *A*: data from a neuron with delay activity in both memory and visual trials. *B*: data from another neuron with delay activity in both memory and visual trials. *C*: data from a neuron with delay activity only in memory trials. *D*: data from a neuron with delay activity only in visual trials.

## RESULTS

### Presence of delay activity in FEF output neurons

We studied 66 FEF output neurons that projected to the SC as determined by antidromic stimulation. Of these, 51 (77%) had significant delay activity, i.e., their mean firing rates in the Delay epoch were greater than (42 neurons) or less than (9 neurons) their mean firing rates in the Base 1 epoch during one or more trial types. Figure 2 shows data from four FEF output neurons to illustrate various types of activity profiles that we found. For simplicity in illustrating these types, we only show trials in which the monkey was required to make a saccade (Go trials). In each panel, memory trial results are shown in the upper data set and visual trial results in the lower data set. Neuronal activity and eye movements are aligned to target onset (*left*), Go instruction onset (*middle*), and the cue to respond (*right*). The shaded boxes highlight the delay activity. Some neurons, as in Fig. 2, *A* and *B*, had delay activity in both memory and visual trials. Others had delay activity only in memory trials (Fig. 2*C*) or only in visual trials (Fig. 2*D*).

Table 2 summarizes the overall distribution of neurons. Of the 51 FEF output neurons having delay activity, 32 (63%) were similar to the neurons shown in Fig. 2, *A* and *B*, in that they had delay activity in both memory and visual trials (Table 2, *top row total*). Another 7 neurons (14%) were similar to the neuron shown in Fig. 2*C* in that they had delay activity in memory trials only (Table 2, *middle row total*). The remaining 12 neurons (24%) were similar to the one shown in Fig. 2*D* in that they had delay activity in visual trials only (Table 2, *bottom row total*). Thus many FEF output neurons had delay

activity between stimulus and response, as we reported previously (Sommer and Wurtz 2000), and in individual neurons the activity could occur in memory trials, visual trials, or both. The next step was to see if the delay activity was influenced by movement instructions, which was done by comparing data from Go versus Nogo trials.

### Delay activity modulated by movement instructions

Figure 3 shows data from the same neurons as in Fig. 2, but now activity in Go trials (blue) is contrasted with that in Nogo trials (orange). If a neuron's delay activity differed significantly in Go versus Nogo trials during one or more trial types,

TABLE 2. Distribution of FEF output neurons that have delay activity

	Go/Nogo Selective* in				Totals
	Memory and visual trials	Memory trials only	Visual trials only	Not Go/Nogo Selective	
Delay activity in					
Memory and visual trials	11†	8	2	11	32
Memory trials only	—	5	—‡	2	7
Visual trials only	—	—	1	11	12
Totals	11	13	3	24	51

\* Go/Nogo selective neurons had delay activity that differed significantly in Go versus Nogo trials. † Values are numbers of neurons. ‡ —, locations in the table that were not applicable; for example, if a neuron had delay activity in memory trials only, it could not have been Go/Nogo selective in visual trials only (because Go/Nogo selectivity is a property of delay activity).

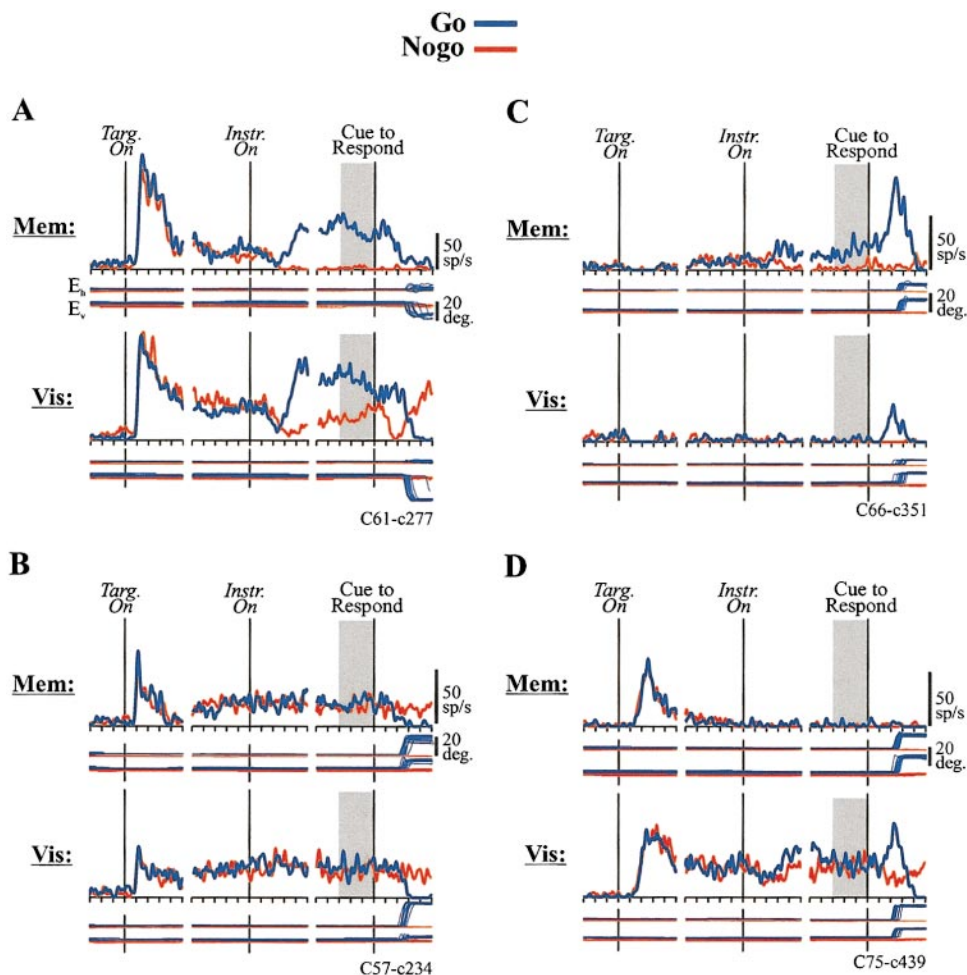


FIG. 3. Delay activity during Go versus Nogo trials. These data are from the same neurons shown in Fig. 2, but now data from Go trials (blue) and Nogo trials (orange) are compared. Spike density functions summarize the firing rates and below them are eye position traces from Go and Nogo trials. *A*: data from a neuron having Go/Nogo selective delay activity in *both* memory and visual trials. *B*: data from a neuron having delay activity in both memory and visual trials, but for this neuron the activity was *not* Go/Nogo selective in either trial type. *C*: data from a neuron having Go/Nogo selective delay activity only in memory trials. *D*: data from a neuron having delay activity that was not Go/Nogo selective and that appeared only during visual trials.

we termed the neuron *Go/Nogo selective*. We found a total of 27 FEF output neurons that were Go/Nogo selective (see Table 2, *first three columns*). The neuron shown in Fig. 3A, for example, was Go/Nogo selective in that it had greater delay activity (shaded boxes) after Go instruction than after Nogo instruction. This neuron was Go/Nogo selective in memory trials (upper data set) and in visual trials (lower data set). As shown in Table 2 (*first column*), a total of 11 neurons were similar in that they were Go/Nogo selective in both memory and visual trials.

We also found some neurons that were Go/Nogo selective in memory trials only (Table 2, *second column*) or in visual trials only (Table 2, *third column*). The neuron shown in Fig. 3C, for example, had delay activity in memory trials only and this activity was modulated by movement instructions; a total of 5 neurons were similar (Table 2, intersection of *middle row* and *second column*). Another 8 neurons had delay activity in both memory and visual trials but the activity was influenced by movement instructions only during the memory trials (Table 2, intersection of *top row* and *second column*). Thus 13 neurons were Go/Nogo selective in memory trials only (Table 2, *second column* total). Another 3 neurons were Go/Nogo selective in visual trials only (Table 2, *third column* total).

Delay activity could be modulated by movement instructions in two possible ways: the activity could be relatively larger in Go trials (Fig. 3, A and C) or in Nogo trials (e.g. Fig. 4). Most of the Go/Nogo selective neurons had delay activity that was larger

in Go trials (74%, 20/27); we termed these neurons *Go selective*. The remaining neurons (26%, 7/27) had greater activity in Nogo trials; we termed these neurons *Nogo selective*.<sup>1</sup>

In summary, we found that movement instructions influenced delay activity in 53% (27/51) of FEF output neurons. We found a variety of neuron types; some neurons were Go/Nogo selective in both memory and visual trials ( $n = 11$ ), others were Go/Nogo selective in memory trials only ( $n = 13$ ), and a few were Go/Nogo selective in visual trials only ( $n = 3$ ). In most neurons the delay activity was specifically *Go* selective, i.e., preferentially activated by Go instruction, but in some neurons the activity was *Nogo* selective, i.e., preferentially activated by Nogo instruction.

We emphasize that, at this point in our analysis, two hypotheses about the data are valid. The Go/Nogo selective delay activity could be purely *instruction*-related, literally representing the movement instruction and therefore signaling the concepts “go” or “do not go” in general. Alternatively, the activity might be *motor*-related, representing the specific upcoming motor response (generation or suppression of a particular vec-

<sup>1</sup> Also, recall that for some neurons delay activity was represented as a decrease in firing rate relative to baseline; such neurons were *Go* selective if they had a greater decrease in activity in Go than in Nogo trials (this accounted for 2 of the 20 *Go* selective neurons) and *Nogo* selective if they had a greater decrease in activity in Nogo than in Go trials (this accounted for 1 of the 7 *Nogo* selective neurons).

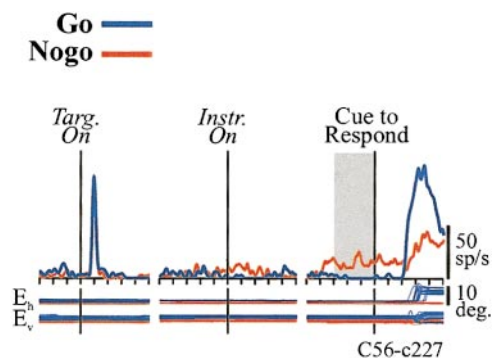


FIG. 4. Data from an example Nogo selective neuron. Nogo selective neurons had greater delay activity in Nogo trials than in Go trials. Conventions are as in Fig. 3 except that, for simplicity, only memory trials are shown.

tor of saccade). We evaluate these competing hypotheses later in the RESULTS.

#### Delay activity related to the visual stimulus

We also found 24 FEF output neurons that had delay activity that was not affected by Go/Nogo instructions (Table 2, *fourth column*). In these neurons, delay activity seemed to be unrelated to future movement and therefore it was instead probably related to the visual stimulus. The neuron shown in Fig. 3B, for example, had delay activity that was unaffected by Go versus Nogo instructions, and this activity occurred in both memory and visual trials. A total of 11 neurons were similar (Table 2, intersection of *top row* and *fourth column*). The delay activity of these neurons seemed to represent the fact that a visual stimulus had appeared regardless of whether the stimulus subsequently disappeared or remained present. Another 2 neurons had delay activity that was unaffected by Go/Nogo instructions, and this delay activity occurred only in memory trials (Table 2, intersection of *middle row* and *fourth column*). In these neurons, delay activity seemed to be exclusively related to memory of the stimulus. The remaining 11 neurons had delay activity that was unaffected by Go/Nogo instructions, and this activity occurred only in visual trials (Table 2, intersection of *bottom row* and *fourth column*). An example of such a neuron is shown in Fig. 3D. In these neurons, delay activity seemed to be a simple tonic visual response.

Thus we found that movement instructions did *not* influence delay activity in 47% (24/51) of FEF output neurons. The delay activity of these neurons seemed to be entirely related to the visual stimulus. There was a variety of neuron types: some neurons had delay activity in both memory and visual trials ( $n = 11$ ), a few neurons had delay activity in memory trials only ( $n = 2$ ), and the rest had delay activity in visual trials only ( $n = 11$ ).

#### Spatiotemporal characteristics of delay activity

To further characterize delay activity, we analyzed its temporal attributes (for Go/Nogo selective neurons) and its spatial attributes (for all neurons). First we asked the following question regarding Go/Nogo selective neurons: after the instruction and the target were presented, when did the neuronal activity begin to diverge in Go versus Nogo trials? The time course of Go/Nogo divergence was quantified by measuring mean firing rates during eight successive 100-ms epochs after both the target and the instruction had appeared, as illustrated for one

neuron (Fig. 5A). For this example, the instruction occurred after the target; therefore the eight analysis epochs began at instruction onset. Figure 5B shows the mean firing rates (and SEs) following instruction onset during each of the eight epochs; also, activity during the Base 1, Base 2, and Delay epochs are shown for reference. We compared the firing rates in Go versus Nogo trials within each epoch; asterisks identify Go/Nogo pairs that were significantly different ( $P < 0.05$ ). For this example, the earliest point at which Go and Nogo firing rates diverged was 400–500 ms after instruction onset.

To find the average time of divergence across the sample of neurons, it was not useful to pool the raw data because mean delay activity firing rates of the different neurons varied over a broad range, from near zero to almost 140 spikes/s. Therefore we normalized the firing rates of each neuron that had Go/Nogo selective delay activity and averaged the normalized data. Figure 5B depicts the normalization procedure graphically, with raw firing rates labeled on the left ordinate and normalized firing rates labeled on the right ordinate. We transformed each neuron's firing rates so that the mean delay activity for the instruction signaled by the neuron (e.g., Go for a Go selective neuron) equaled 1.0 and the mean delay activity during the other instruction (e.g., Nogo for a Go selective neuron) equaled 0.0. We linearly adjusted the firing rates during all other time periods to this scale. Figure 5C shows the average normalized time courses for all neurons having Go/Nogo selective delay activity; zero on the abscissa is the time of the second task event, i.e., the time of instruction onset in target-first trials (see Fig. 1C) or the time of target onset in instruction-first trials (Fig. 1D). We found that, on average, Go and Nogo firing rates began to diverge 300–400 ms after both the target and the instruction were presented.

Next, we analyzed the spatial organization of delay activity by comparing neuronal responses with targets presented in different locations in the visual field. This was important for testing whether the delay activity might be related to nonspatial phenomena (e.g., expectation of reward). Before starting formal data collection on a neuron, we always had monkeys perform the Go/Nogo task for several trials using targets presented not only within the visual and/or movement field but also at an isocentric, opposite direction location to see if there was any hint of delay activity for *both* directions. Of the 51 neurons with delay activity, 31 clearly had no delay activity when targets were presented opposite to the visual and/or movement field. For these neurons, we used only the target location within the visual and/or movement field during formal data collection. For the remaining 20 neurons, we randomly interleaved both target locations during formal data collection and found that 12 of them had delay activity only for targets presented in the visual and/or movement field whereas 8 had delay activity for both locations of the target. In sum, delay activity was spatially selective in 84% of the neurons (43/51), which suggests that the activity was primarily related to stimulus or response, both of which are spatially localized, and was generally unrelated to nonspatial phenomena.

We also examined, in neurons having Go/Nogo selective delay activity, whether the difference in activity in Go versus Nogo trials occurred only if saccades were made into a restricted region of visual space. If true, this would show that the difference in activity was specifically motor-related, i.e., associated with making specific vectors of saccades, and not purely instruction-related, i.e., representative of the nonspatial con-



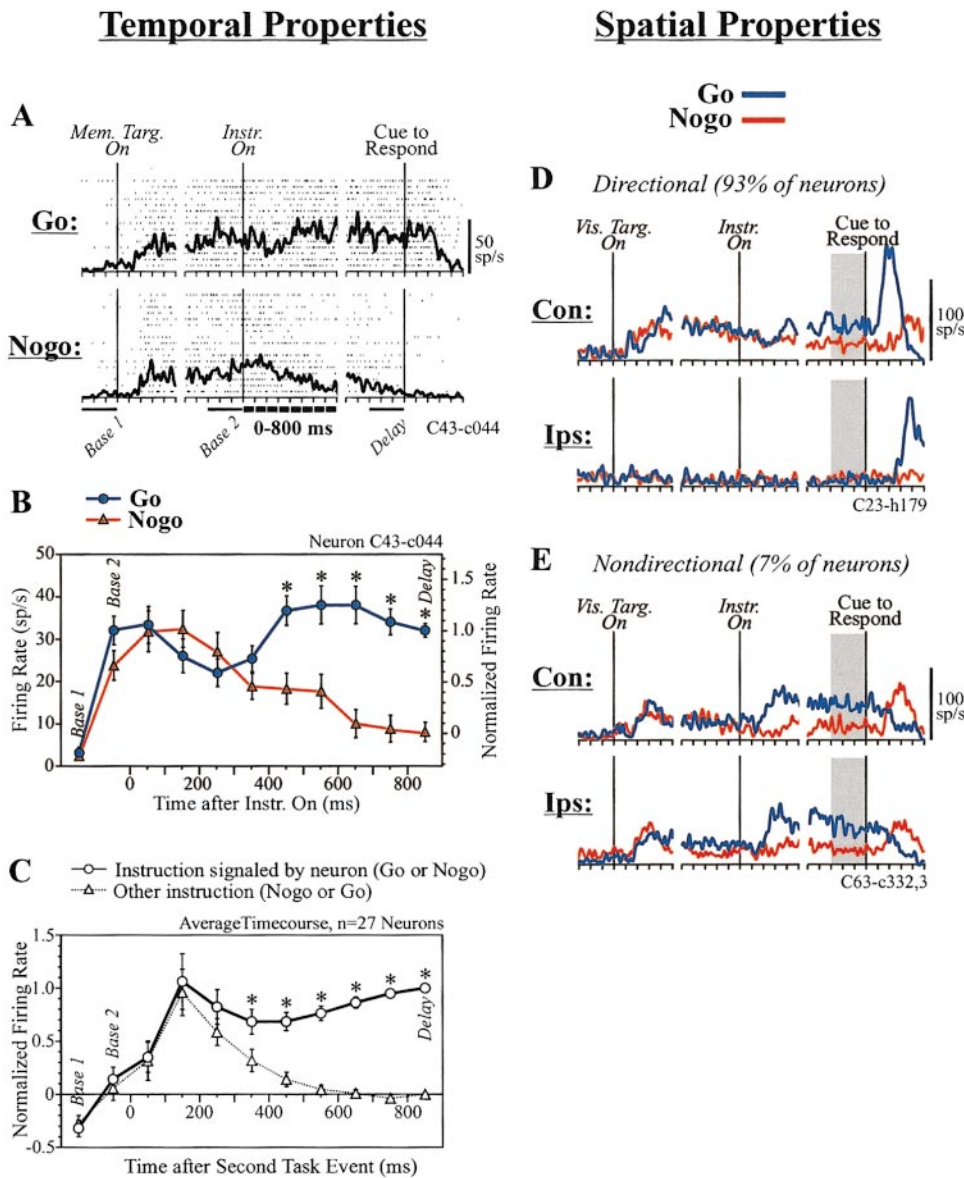


FIG. 5. Spatiotemporal characteristics of Go/Nogo selective delay activity. *Left*: temporal properties; *right*: spatial properties. *A*: to illustrate the time course analysis, data from an example neuron are shown, aligned to target onset (*left*), instruction onset (*middle*), and the cue to respond (*right*). Mean firing rates were calculated during 11 epochs: during 8 successive 100-ms epochs following the second task event (thick lines at bottom) and during the Base 1, Base 2, and Delay epochs (thin lines at bottom). *B*: firing rates (mean and SE) during the 11 epochs for the neuron shown in *A* are graphed. Left ordinate shows raw firing rate in spikes per second (sp/s); right ordinate shows the normalized firing rate such that mean delay activity in Go trials = 1 and mean delay activity in Nogo trials = 0. Legend at top. Base 1 and Base 2 epoch firing rates are at the far left and the Delay epoch firing rate is at far right. Between are the firing rates from 0 to 800 ms after the second task event, i.e., instruction onset. Each datum from 0–800 ms is placed at the midpoint of the 100-ms sampling bin (i.e., every 50 ms). \*, time points at which Go and Nogo firing rates differed from each other. *C*: overall time course of Go/Nogo selective delay activity. Data from the 27 neurons having Go/Nogo selective delay activity were pooled. Firing rates for each neuron were normalized as shown for the example in *B* and the normalized firing rates of the 27 neurons were averaged within each epoch. Legend at top. As in *B*, \* marks time points when Go and Nogo signals differ. *D*: example of a neuron for which Go/Nogo selectivity was *directional*, which is representative of 93% of the neurons having Go/Nogo selective delay activity. Spike density functions summarize the neuron’s activity in Go and Nogo trials (legend at top), for contralateral target presentation (within the neuron’s movement field) (Con, upper data set), and for ipsilateral target presentation (Ips, lower data set). Delay activity (shaded boxes) was significant and was different in Go versus Nogo trials only for contralateral target presentation. *E*: example of a neuron for which Go/Nogo selectivity was *nondirectional*, which is representative of 7% of neurons having Go/Nogo selective delay activity. This neuron had an omnispacial visual receptive field (it responded to both contralateral and ipsilateral target presentation) and had elevated delay activity in Go versus Nogo trials for targets presented both contra- and ipsilaterally. Sp, spikes.

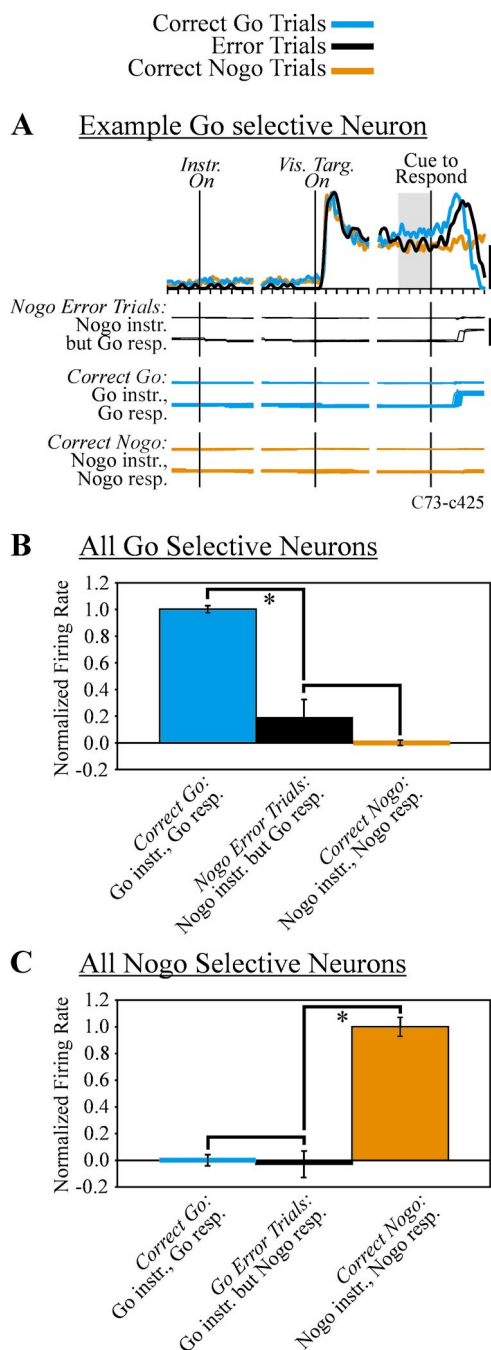
cepts “go” or “do not go.” Of the 27 neurons with Go/Nogo selective delay activity, 18 clearly were inactive when targets were presented opposite to the visual and/or movement field. For the remaining 9 neurons, we randomly interleaved both

target locations during formal data collection and found that 7 of them had Go/Nogo selective delay activity *only* when saccades were made to targets presented inside the visual and/or movement field (e.g., Fig. 5D) whereas 2 neurons were non-



directional, having Go/Nogo selective delay activity for saccades made to both locations of the target (e.g., Fig. 5E). In sum, this analysis indicated that Go/Nogo selective delay activity primarily was motor-related because it was associated with making a restricted range of saccades in 93% (25/27) of the neurons.

To summarize, our analysis of spatiotemporal properties of delay activity in FEF output neurons revealed that 1) Go/Nogo selective delay activity started to differ in Go versus Nogo trials about 300–400 ms after both the instruction and the target were presented, 2) most of the delay activity was spatially restricted, and 3) nearly all of the Go/Nogo selectivity seemed to be motor-related, because it was associated with making a restricted range of saccades.



### Relationship between Go/Nogo selective delay activity and saccade initiation

We performed two analyses to determine the extent to which Go/Nogo selective delay activity was related to actual initiation of a saccadic eye movement. First, to see if the activity might contribute to the timing of the saccadic response, we tested whether the intensity of delay activity predicted *when* a saccade would occur. Second, we tested whether the difference in delay activity in Go versus Nogo trials *always* predicted that a saccade would be initiated, even in error trials. This would reveal whether the Go/Nogo difference in delay activity was a *command*, inevitably leading to a particular motor response, or if it was more of a *suggestion*, providing information to downstream motor centers that could be used or ignored.

First, we examined the relationship between delay activity and *when* a saccade occurred. We performed 54 correlations between delay activity firing rate and reaction time in correct Go trials (27 Go/Nogo selective neurons  $\times$  2 data sets each, i.e., visual and memory trials) with the Pearson product-moment correlation test, as was done in previous reports that compared neuronal activity to reaction time (e.g., Everling and Munoz 2000; Riehle and Requin 1993). After omitting spurious cases of correlation caused by single outlying data points, we found only three significant correlations. Because this number matched the expected false positive rate of 2.7 (54 correlations  $\times$  0.05 criterion level), we concluded that the level of delay activity was not related to when a saccade occurred.

Second, we examined whether the Go/Nogo difference in delay activity *always* predicted the motor response, even in error trials. Figure 6A shows data from a session in which a Go selective neuron was studied; *top*, spike density functions; *bottom*, eye traces. The saccadic responses made by the monkey in Nogo error trials (black eye traces) were nearly identical to the responses during correct Go trials (blue eye traces). For comparison, responses during correct Nogo trials (orange eye traces) also are shown. The question was, Did the delay activity in Nogo error trials resemble the delay activity in correct Go trials, thereby demonstrating that delay activity faithfully predicted saccade generation? The answer was no. In the spike density functions it can be seen that the delay activity (shaded box) during Nogo error trials (black) was *not* identical to that during correct Go trials (blue); rather, it overlapped with the delay activity in correct Nogo trials (orange). In error trials,

FIG. 6. Go/Nogo selective delay activity during error trials. Color legend for all data is at top. The type of response (resp.) and the instruction (instr.) that occurred during each kind of correct and error trial is always noted explicitly. **A:** error and correct trial data collected while recording from a Go selective neuron. Spike density functions are shown above and eye traces below. Data are shown separately for Nogo error trials ( $n = 2$ ), for correct Go trials ( $n = 15$ ), and for correct Nogo trials ( $n = 16$ ). In all pairs of eye traces, the upper eye trace is the horizontal component and the lower eye trace is the vertical component. Scale bars at right represent 100 spikes/s (upper) and  $20^\circ$  (lower). **B:** error trial analysis for the pooled data from all 20 Go selective neurons. Normalized firing rate of delay activity (mean and SE) is graphed for Nogo error trials ( $n = 11$ ), correct Go trials ( $n = 673$ ), and correct Nogo trials ( $n = 736$ ). Delay activity during Nogo error trials was significantly lower than delay activity during correct Go trials (\*) but was not significantly different from delay activity during correct Nogo trials. **C:** error trial analysis for the pooled data from all 7 Nogo selective neurons. For this population, delay activity during Go error trials ( $n = 5$ ) was different from delay activity during correct Nogo trials ( $n = 200$ ) but was indistinguishable from delay activity during correct Go trials ( $n = 187$ ). In neither case (**B** or **C**) did delay activity in error trials predict the motor response; rather, it reflected the instruction that was given.

therefore, the delay activity seemed to reflect the instruction instead of predicting the actual motor response.

Because error trials were rare, occurring in only 1.5% of trials, we could not analyze the data quantitatively for any individual neuron (e.g., only 2 error trials occurred while we recorded from the neuron illustrated in Fig. 6A). Therefore, to analyze error trials quantitatively, we examined the population data. We normalized each neuron's firing rates (see Fig. 5B) and then pooled the data from all 20 Go selective neurons; the result is shown in Fig. 6B. As was suggested by the single neuron example (Fig. 6A), the population delay activity during Nogo error trials (Fig. 6B, black bar) was lower than that during correct Go trials (blue bar) and was indistinguishable from that during correct Nogo trials (orange bar) (ANOVA followed by Dunn's pairwise multiple comparison test,  $P < 0.05$  criteria). Therefore, in this sample, the delay activity reflected the instruction that was given instead of predicting the actual motor response that was made.

We also performed the same analysis on the sample of seven Nogo selective neurons, with similar results. Delay activity during Go error trials (Fig. 6C, black bar) was significantly lower than that during correct Nogo trials (orange bar), even though the motor response in both cases was identical (i.e., steady fixation). However, the delay activity during Go error trials (Fig. 6C, black bar) was indistinguishable from that during correct Go trials (blue bar). In other words, the delay activity again represented the instruction that was given and failed to predict the motor response that was made. Due to the rarity of error trials, we could not analyze any additional sets of data (i.e., Go error trials for Go selective neurons or Nogo error trials for Nogo selective neurons).

In sum, we found that Go/Nogo selective delay activity was a poor predictor of actual saccadic initiation. The intensity of delay activity was not related to reaction time, which suggested that the activity played no role in the timing of saccade generation. Also, the difference in delay activity in Go versus Nogo trials failed to predict the motor response in error trials, which suggested that the delay activity provided information about a desired motor response but was not a command that inevitably caused a particular motor response.

### Short-latency visual responses

Many FEF neurons have an enhanced short-latency response to the onset of a visual target if that target is to be foveated by a saccade (Goldberg and Bushnell 1981; Schall 1991; Wurtz and Mohler 1976), and Everling and Munoz (2000) recently found this enhancement effect in FEF neurons that project to the SC. We therefore searched for this effect in our neurons by analyzing instruction-first trials (see Fig. 1D) to see whether short-latency visual responses to a target's onset differed after the monkey had received Go versus Nogo instruction. Neurons had a short-latency visual response to target onset if their mean activity in the Visual epoch differed significantly from their activity in the immediately preceding Base 2 epoch; 43 of the 66 neurons (65%) had a short-latency visual response. The response was a relative increase in activity for 32 neurons and a relative decrease for 11 neurons. The visual response differed in Go versus Nogo trials for only 5 of 86 cases analyzed (43 neurons  $\times$  2 trial types, i.e., visual or memory trials; Fig. 7A). The only Go selective visual response that we found is illustrated in Fig. 7D (its data point is labeled *d* in Fig. 7A). The

number of Go or Nogo selective visual responses that we found, five, was not much greater than the number expected by chance (false positive rate: 86 cases  $\times$  0.0167 criterion level = 1.4). To confirm this negative result, we analyzed the data using two other methods as well. First, we measured mean firing rate from 0–50 ms following the start of the visual-related burst as detected on a trial-by-trial basis (Hanes et al. 1995; Schall et al. 1995). Of the 43 neurons with a short-latency visual response, 28 could be analyzed using this method (they had a strong enough burst to be detectable in individual trials) and two cases of Go selective visual responses were found (Fig. 7B; an example is shown in Fig. 7E and labeled *e* in Fig. 7B). The expected false positive rate was 0.9 (28 neurons  $\times$  2 trial types each  $\times$  0.0167 significance criterion), however, and therefore the result was not compelling. The second alternate method was to use spike density functions to focus on firing rates very close to the peak discharge. To permit comparison with the results of Everling and Munoz (2000), we replicated their analysis as closely as possible.<sup>2</sup> The results were similar to those found with the other two analysis methods: of 20 cases analyzed (10 neurons  $\times$  2 trial types each), we found two cases of Go or Nogo selectivity (Fig. 7C), which was close to the expected false positive rate of 0.3 (20 cases  $\times$  0.0167 significance criterion). Figure 7F shows the averaged spike density functions for the neurons; the functions overlapped in Go and Nogo trials. In sum, short-latency visual responses of the neurons were rarely influenced by Go versus Nogo instructions.

## DISCUSSION

### Delay activity of FEF output neurons

Delay activity within the prefrontal cortex has been scrutinized during the past three decades (reviewed by Fuster 1997) because it is likely that it plays critical roles in movement, memory, and vision. How the delay activity of prefrontal neurons is used in the overall system that controls voluntary movement, however, is still unknown. Is delay activity used only *locally* within the prefrontal cortex or does some of it *leave* the prefrontal cortex to influence neurons elsewhere? Pioneering studies inferred that delay activity may leave the prefrontal cortex because delay activity in other cerebral regions changed when the prefrontal cortex was cooled (Chafee and Goldman-Rakic 2000; Fuster et al. 1985; see also Tomita et al. 1999). Moreover, two studies of FEF neurons that project to the SC *explicitly* showed that some delay activity leaves the prefrontal cortex (Segraves and Goldberg 1987; Sommer and Wurtz 2000). In the present study, our goal was to systematically characterize this efferent delay activity. To do this we trained monkeys to perform a Go/Nogo task that manipulated whether a saccade had to be made and whether a visual stimulus remained visible or had to be remembered.

<sup>2</sup> We analyzed Visuomotor neurons only (identified in Sommer and Wurtz 2000), constructed spike density functions for the data ( $\sigma = 20$  ms), found the peak time of the visual response 70–140 ms after target onset and excluded neurons if their peak visual response occurred outside this range, used the spike density functions to calculate the mean firing rate from 5 ms before to 5 ms after the peak for each neuron, and subtracted from this value the average prestimulus activity 40–50 ms after target onset. We excluded neurons if this final value of the visual response was  $\leq 20$  spikes/s or if the average peak saccade-related discharge (also calculated using spike density functions of  $\sigma = 20$  ms) was  $\leq 20$  spikes/s above the immediately preceding delay epoch activity.

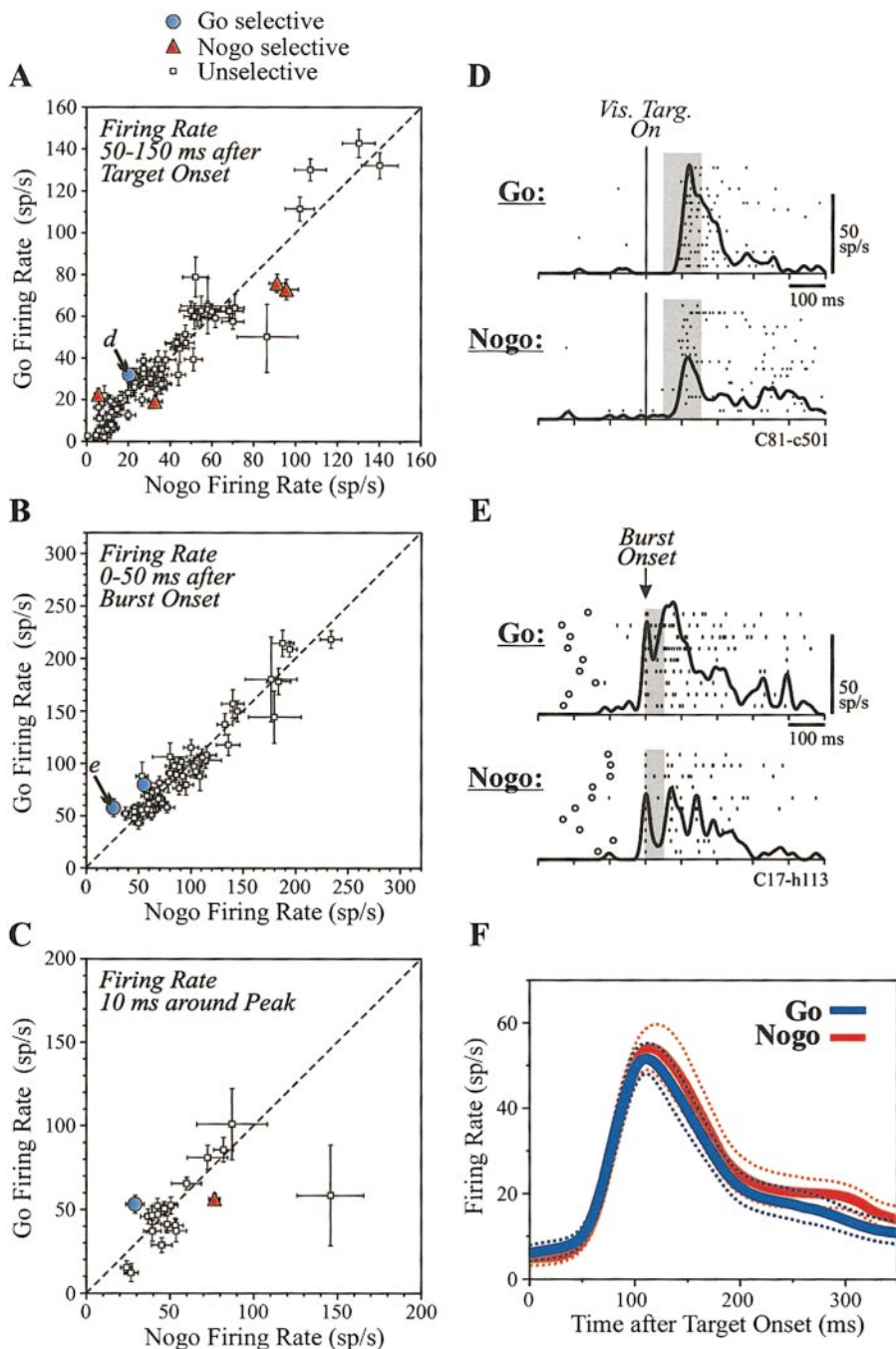


FIG. 7. Effect of Go/Nogo instructions on short-latency visual responses. *A*: mean firing rates (and SEs) 50–150 ms after target onset are plotted for Go trials (ordinate) versus Nogo trials (abscissa) for neurons with a significant short-latency visual response. *d*, data from the example neuron shown in *D*. Sp, spikes. Symbols show whether the activity was Go selective, Nogo selective, or unselective (legend at top). Dashed line is unity line. *B*: activity during the first 50 ms after visual burst onset is plotted for Go versus Nogo trials. *e*, data from the example neuron shown in *E*. *C*: visual response in Go versus Nogo trials calculated using the method of Everling and Munoz (2000). *D*: example activity from the only neuron with a Go selective visual response as revealed using the mean response 50–150 ms after target onset (cf. *A*). Shading depicts the analysis epoch. *E*: example activity from one neuron with a Go selective visual response as detected during the first 50 ms after burst onset (cf. *B*). Rasters and spike density functions are aligned to the first spike in the visual-related burst and visual target onset times are indicated with  $\circ$ . Shading depicts the analysis epoch. *F*: average spike density functions from the neurons analyzed using the Everling and Munoz (2000) method (cf. *C*). Means are shown with thick lines and these are surrounded by thin dashed lines representing the SE.

Our most fundamental result was that the delay activity of FEF output neurons was remarkably diverse, as illustrated in Table 2. Because the delay activity was not uniform in its properties from neuron to neuron, we reject the possibility that the activity plays only a single role in visuosaccadic behavior. Instead, we think that various types of delay activity play a variety of roles. In our view, there were six important classes of delay activity in our sample that may be related to possible functions (Table 3). These six classes were those that we noted in RESULTS: delay activity that was Go/Nogo selective in both memory and visual trials, in memory trials only, or in visual trials only, and delay activity that was *not* Go/Nogo selective and that occurred in both memory and visual trials, in memory trials only, or in visual trials only.

First, in 22% (11/51) of the FEF output neurons, delay activity was Go/Nogo selective in both memory and visual trials (Table 3, item 1). We think that this type of delay activity generally signaled where to make the next saccade because 1) the activity differentiated between Go and Nogo instructions at an appropriate time, i.e., after the target and instruction were presented but before the cue to respond was given; 2) the activity preceded only a restricted range of saccadic vectors, which showed that it was related to where the saccade went; 3) the activity did not predict reaction time, which suggested that it did not signal *when* the saccade should occur; and 4) the activity was Go/Nogo selective regardless of whether or not a visual target was present, which suggested that it was related to saccades in general and not to saccades made in specific task



TABLE 3. Putative functions of delay activity in FEF output neurons

Observed Properties	Putative Function
<i>Go/Nogo selective (related to the impending movement)</i>	
1. Go/Nogo selective in both memory and visual trials (22%)	Representation of where to move
2. Go/Nogo selective in memory trials only (25%)	Working memory
3. Go/Nogo selective in visual trials only (6%)	Attentional modulation of visual response
<i>Not Go/Nogo selective (related to the visual stimulus)</i>	
4. Delay activity occurred in both memory and visual trials (22%)	Representation of a location in visual space
5. Delay activity occurred in memory trials only (4%)	Transient visual memory
6. Delay activity occurred in visual trials only (22%)	Simple tonic visual response

Values in parentheses show the frequency of occurrence of each neuron type as a percentage of the 51 FEF output neurons that had delay activity. Sum of the percentages does not equal 100% due to round-off error.

contexts. Although the delay activity provided information about where to move, it did not appear to be an absolute command to move because the activity did not predict the motor response during error trials. Characterizing this efferent delay activity as representing where to move is consistent with a previous hypothesis, arising from electrical stimulation results, that the output of FEF contains a “retinotopic goal that is converted by a downstream structure into the vector of the eventual saccade” (Dassonville et al. 1992, p. 300).

Second, in 25% (13/51) of the FEF output neurons, delay activity was Go/Nogo selective in memory trials only (Table 3, item 2). We think that this delay activity represented working memory of the target location, where working memory is defined as the temporary storage of information for the purpose of performing a task (for reviews see Izquierdo et al. 1999 and Richardson 1996). Accordingly, delay activity was present in memory trials when a Go instruction cued the monkey that remembering the target location was critical (because a saccade would have to be made to the location), but this delay activity was attenuated when a Nogo instruction cued the monkey that remembering the target location was moot (because no saccade would have to be made). These criteria for identifying delay activity as a correlate of working memory are similar to, but more restrictive than, the criteria of others (e.g., Funahashi et al. 1989; see Goldman-Rakic 1995) who required that the activity occur in memory trials but who did not systematically test whether the activity was attenuated when memory became irrelevant. Our interpretation that FEF output signals represent working memory is consistent with the results of lesion and reversible inactivation studies which showed that FEF activity is crucial for the ability to make saccades to remembered target locations (e.g., Deng et al. 1986; Sommer and Tehovnik 1997).

Third, in 6% (3/51) of the FEF output neurons, delay activity was Go/Nogo selective in visual trials only (Table 3, item 3). This delay activity was a response to a visible target that was modulated by the requirement to look at the target and, therefore, we think that this activity was a correlate of spatial visual attention. Our limited sample of these neurons, however, precludes a more detailed discussion of them.

Fourth, in 22% (11/51) of the FEF output neurons, delay activity was *not* Go/Nogo selective and the activity appeared in both memory and visual trials (Table 3, item 4). Because this delay activity was not influenced by impending movement, it seemed to be entirely related to the visual stimulus. Furthermore, because it usually was directional it seemed to represent the location of the stimulus and because it occurred in both memory and visual trials it seemed to represent the location of the stimulus *regardless* of whether the actual stimulus remained there or disappeared. Therefore we think this type of delay activity represented a coordinate in visual space. This type of delay activity may be an intermediary stage in visuo-motor transformation in that the activity is independent of continued visual input but does not yet carry any information about impending movement.

Fifth, in 4% (2/51) of the FEF output neurons, delay activity was not Go/Nogo selective and the activity appeared in memory trials only (Table 3, item 5). This activity, although exclusively related to remembering a visual stimulus, did not seem to represent a working memory signal because it was not attenuated in Nogo trials when memory of the target location became irrelevant. Therefore, we suggest that this activity represented an obligatory type of transient visual memory, a signal that temporarily represented the location of the target regardless of whether this information was needed for the task.

Sixth, in 22% (11/51) of the FEF output neurons, delay activity was not Go/Nogo selective and occurred in visual trials only (Table 3, item 6). This type of delay activity clearly seemed to be a tonic visual response. Therefore, some of the delay activity of FEF output neurons seems to represent the current visual scene [more precisely, the scene one afferent lag time (~100 ms) prior].

In these discussions of various types of Go/Nogo selective delay activity, we implicitly focused on the majority of FEF output neurons having *Go* selective delay activity. In some neurons, however, the delay activity was *Nogo* selective, related to not moving the eyes. We suggest that Nogo selective neurons played complementary roles to Go selective neurons, acting to *suppress* signals related to representing where to move, to working memory, and to visual attention, so as to prevent saccade generation.

In our previous study of FEF output signals (Sommer and Wurtz 2000), we concluded that signal flow from the FEF to the SC may be modeled as a continuous multistage system in that signals from every stage in the visuomotor transformation, including visual-related bursts of activity, delay activity, and saccade-related bursts of activity, all are transmitted in the projection. In the present study, we focused on the *middle* of this visuomotor transformation and found that delay activity in the output of the FEF is related to vision, memory, and impending movement. Our present findings therefore extend our prior model of FEF output, showing that signals representing successive stages of visuomotor transformation are sent to the SC even during delay periods between stimulus and response.

#### Short-latency visual responses of FEF output neurons

We examined whether short-latency visual responses of FEF output neurons were influenced by Go/Nogo instructions. For the most part they were not. This was surprising because enhancement of phasic visual responses has been induced

previously using Go/Nogo instructions (Schall 1991) and has been found in SC-projecting FEF neurons (Everling and Munoz 2000). We note, however, that in all studies finding enhancement of FEF visual responses, saccades were made immediately after visual stimulation with no imposed delay (Burman and Segraves 1994; Everling and Munoz 2000; Goldberg and Bushnell 1981; Schall 1991; Wurtz and Mohler 1976). In contrast, saccades were purposefully delayed in our study. It may be that saccadic enhancement of short-latency visual responses requires the close proximity of the visual burst to saccade initiation so that our lack of enhancement was caused by the delay period in our task.

#### *Previous studies of FEF neurons projecting to the SC*

Two previous studies also described signals related to impending saccades that course from the FEF to the SC. First, Segraves and Goldberg (1987) found that 4% (2/51) of their SC-projecting FEF neurons had “anticipatory” delay activity that apparently was related to making a saccade (see their Fig. 11). However, they did not report the detailed characteristics of this activity, in particular, whether the activity decreased if saccade production was not required and whether the activity might be related to memory or to vision. Second, Everling and Munoz (2000) studied how activity in the projection from the FEF to the SC varied with movement instructions, but they did not study delay activity. Rather, they examined activity occurring *before* a target appeared, with the goal of understanding how initial “set” activity was related to the reaction time of responding to the target. They found that, during an initial fixation period, the averaged, pooled response of their FEF output neurons was greater when a monkey was instructed to look at an upcoming target as opposed to looking away from it. Because the upcoming target location was randomized, this instruction-related activity was not associated with a particular target location or saccade direction. Their nondirectional, instruction-related “set” activity, therefore, was quite different from our directional, stimulus- or movement-related delay activity.

#### *Role of the prefrontal cortex in the control of voluntary movement*

The signals that we described go to the SC, mostly to its intermediate layers (Stanton et al. 1988). Many intermediate-layer SC neurons exhibit long-lead tonic activity prior to restricted ranges of saccadic movements (Ma et al. 1991; Mohler and Wurtz 1976; Schiller and Koerner 1971; Wurtz and Goldberg 1972). Much of this activity is strongly related to impending movement in that it is modulated by instructions to move (Glimcher and Sparks 1992) and by the probability that a movement will be made into the neuron’s movement field (Basso and Wurtz 1998). Intensity of the activity is related to reaction time (Basso and Wurtz 1998) and to making saccades both in correct and in error trials (Glimcher and Sparks 1992). These studies have been complemented by investigations of *gap activity*, i.e., tonic activity that occurs after a foveated spot disappears and before a peripheral saccadic target appears. Gap activity in the SC is strongly movement-related in that its intensity predicts both reaction time and the occurrence of saccades

in both correct and error trials (Dorris and Munoz 1998; Dorris et al. 1997; Everling et al. 1998, 1999). Gap activity exists in the FEF also but there it is not as closely related to saccade generation (Everling and Munoz 2000; Everling et al. 1999).

In sum, at the *destination* of the projection studied in the present report, the SC, long-lead tonic activity seems to be strongly related to saccade generation. At the *source* of the projection, the FEF, similar tonic activity can be found but it seems to be more weakly linked to saccade generation. *Within* the projection, we found that delay activity leaving the FEF provides the SC with a wealth of signals related to selection of where to move, to working memory, to spatial attention, to selection of a location in visual space, to transient visual memory, and to representation of the current visual scene. These descending signals presumably are used by recipient SC neurons for generating the appropriate saccade. Taken together, these findings suggest that there is a gradual shift in function from the FEF to the SC in which processes that are more directly related to saccade generation increase in prominence.

Finally, we think that the present results have broader implications as well. We hypothesize that a general function of the prefrontal cortex might be to influence motor behavior by sending many types of delay activity related to movement, memory, and vision to more motor-related areas. For the skelletomotor system, these recipient areas would include the premotor and supplementary motor cortices. Intriguingly, it appears that some of the motor-related structures downstream from the prefrontal cortex in turn send delay activity even further downstream. For example, the primary motor cortex sends arm movement-related delay activity into the spinal cord (Tanji and Evarts 1976) and spinal interneurons exhibit similar delay activity (Prut and Fetz 1999). An analogous situation may exist in the oculomotor system, with its motoneurons confined to the brain stem, because tonic, long-lead presaccadic activity is carried by some descending SC efferents (Munoz and Guitton 1991). This distant penetration of movement-related delay activity into the motor system may prime end stage motor circuits (Prut and Fetz 1999) and ultimately accomplish a motor preparatory function that improves the speed and control of motor behavior (see Requin et al. 1991).

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