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Role of Frontal Eye Fields in Countermanding Saccades: Visual, Movement, and Fixation Activity

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Hanes, Doug P., Warren F. Patterson II, and Jeffrey D. Schall. Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. *J. Neurophysiol.* 79: 817–834, 1998. A new approach was developed to investigate the role of visual-, movement-, and fixation-related neural activity in gaze control. We recorded unit activity in the frontal eye fields (FEF), an area in frontal cortex that plays a central role in the production of purposeful eye movements, of monkeys (*Macaca mulatta*) performing visually and memory-guided saccades. The countermanding paradigm was employed to assess whether single cells generate signals sufficient to control movement production. The countermanding paradigm consists of a task that manipulates the monkeys' ability to withhold planned saccades combined with an analysis based on a race model that provides an estimate of the time needed to cancel the movement that is being prepared. We obtained clear evidence that FEF neurons with eye movement-related activity generate signals sufficient to control the production of gaze shifts. Movement-related activity, which was growing toward a trigger threshold as the saccades were prepared, decayed in response to the stop signal within the time required to cancel the saccade. Neurons with fixation-related activity were less common, but during the countermanding paradigm, these neurons exhibited an equally clear gaze-control signal. Fixation cells that had a pause in firing before a saccade exhibited elevated activity in response to the stop signal within the time that the saccade was cancelled. In contrast to cells with movement or fixation activity, neurons with only visually evoked activity exhibited no evidence of signals sufficient to control the production of gaze shifts. However, a fraction of tonic visual cells exhibited a reduction of activity once a saccade command had been cancelled even though the visual target was still present in the receptive field. These findings demonstrate the use of the countermanding paradigm in identifying neural signatures of motor control and provide new information about the fine balance between gaze shifting and gaze holding mechanisms.

INTRODUCTION

Although much is known about the neural circuits involved in saccade generation, little is known about how the decision is made when to shift gaze (Carpenter 1991; Wurtz and Goldberg 1989). The outcome of this decision process, which arises out of the neural balance between gaze-holding and gaze-shifting mechanisms, is either the initiation or withholding of an eye movement. One pronounced expression of behavioral control is canceling a planned movement. In this paper, we introduce a novel behavioral paradigm with which we investigated the neural correlates of these decision processes. The *countermanding paradigm*, which includes both a task design and a specific theoretical construct, was developed to investigate the control of action (e.g., DeJong et al. 1990, 1995; Lappin and Eriksen 1966; Osman et al.

1986, 1990; Vince 1948; reviewed by Logan 1994; Logan and Cowan 1984). A subject's ability to control voluntarily the production of movements is evaluated in a reaction time task by infrequently presenting an imperative *stop signal*. The subject is instructed to withhold the impending movement if the stop signal occurs.

Performance in the countermanding task is probabilistic. In a given trial, one can predict only to a certain extent whether the subject will be able to inhibit a planned movement. The probability of inhibiting a movement decreases as the delay between the signal to initiate the movement and the signal to inhibit the movement, called the stop signal, increases. This unpredictability arises because saccade latency is fundamentally stochastic, varying unpredictably across trials. In principle, one can see that saccades generated with short latencies would occur even if the stop signal was presented because such short-latency saccades would be initiated before the stop signal could influence the system. Likewise, saccades generated with long latencies would be inhibited if a stop signal was presented because their reaction times allow enough time for the stop signal to influence the system thereby canceling the planned saccade. These relationships permit an experimental comparison between trials in which a stop signal was presented and saccade production was inhibited successfully and trials with movements that were made but would have been inhibited had the stop signal been presented (the trials with the long reaction times). By comparing the neural activity in these different trial types, one can investigate the neural mechanisms underlying the gaze-holding and -shifting processes.

This analysis establishes the central benefit of the countermanding paradigm for determining whether single cells generate signals sufficient to control the production of movements. For a neuron to play a direct role in eye movement production, it must discharge differently during trials in which a saccade was initiated as compared with trials in which the saccade was inhibited. Moreover, the difference in activity must occur by the time that the movement was cancelled. Logan and Cowan (1984; see also Logan 1994) showed that the duration required to cancel the movement, known as stop-signal reaction time, can be estimated by implementing a simple race model. Similar ideas were developed independently in the oculomotor literature to analyze performance in double-step saccade tasks (Becker and Jürgens 1979; Lisberger et al. 1975).

We recorded from single cells in the frontal eye fields (FEF) of macaque monkeys performing the countermanding task. FEF is an area in the prefrontal cortex that lies at the interface of visual processing and eye movement production

(reviewed by Bruce 1990; Goldberg and Segraves 1989; Schall 1991b, 1997). Therefore, it is likely that FEF cells play a role in the decision processes that determine if and when a saccade will be produced. Numerous studies of the effects of lesions of FEF have demonstrated that accurate saccades with reasonably normal latencies can be produced after a recovery period (e.g., Lynch 1992; Schiller et al. 1980, 1987) probably through adaptive plasticity mechanisms. It is critical to note, though, that the interpretation of these lesion data is based on the function that recovers during several days or weeks. Most lesion studies report an initial gaze impairment immediately after the lesion, and more recent work has shown quite clearly that inactivation of FEF causes contralateral gaze paralysis (Dias et al. 1995; Sommer and Tehovnik 1997). Even if FEF is not uniquely necessary for saccade production by virtue of its extensive connectivity with the rest of the oculomotor system, neural activity in FEF can be regarded as a reliable index of the state of saccade programming throughout the system.

Some of the findings have appeared previously in abstract form (Schall and Hanes 1996).

METHODS

Subjects and surgery

Data were collected from three *Macaca mulatta* weighing 9–12 kg. The animals were cared for in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals and the guidelines of the Vanderbilt Animal Care Committee. The surgical procedures have been described elsewhere (Hanes et al. 1995; Schall et al. 1995).

Data collection

The experiments were under computer control (PDP 11/83), which presented the stimuli, recorded the eye movements, collected single-unit activity, and delivered the juice reward. Standard techniques were used to collect these data (Hanes et al. 1995; Schall et al. 1995). Single units were recorded using insulated tungsten microelectrodes (1–2 M Ω) that were under the control of a microdrive. Electrodes were inserted through guide tubes positioned in a grid with holes spaced at 1-mm intervals (Crist et al. 1988). The action potentials were amplified, filtered, and discriminated conventionally with a time-amplitude window discriminator and were sampled at 1-kHz resolution. Single units were admitted to the database if the amplitude of the action potential was sufficiently above background to reliably trigger the time-amplitude window discriminator, the action potential waveshape was invariant throughout testing, and the isolation could be sustained for a sufficient period for testing. Saccades were detected using a computer algorithm that searched first for significantly elevated velocity ($>30^\circ/\text{s}$). Saccade initiation and termination then were defined as the beginning and end of the monotonic change in eye position lasting 12 ms before and after the high-velocity gaze shift. On the basis of the 250-Hz sampling rate, this method is accurate to within 4 ms.

Tasks and behavioral training

Detailed descriptions of the behavioral training and tasks have appeared previously (Hanes and Schall 1995). Each animal was tested for ~ 3 h/d, 5 d/wk. During testing, fruit juice was given as positive reinforcement. Access to water in the home cage was controlled and monitored. Fluids were supplemented as needed.

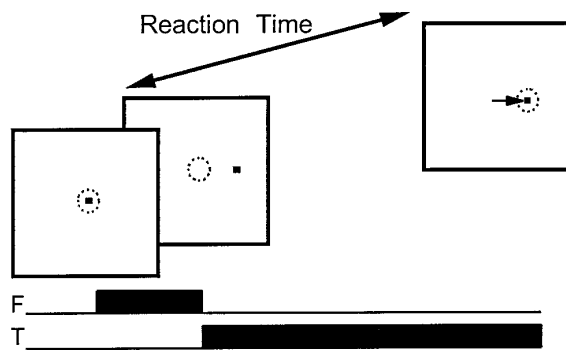
Monkeys were seated in an enclosed chair within a magnetic field to monitor eye position via a scleral search coil. Stimuli were presented on a video monitor ($48^\circ \times 48^\circ$) using computer controlled raster graphics (Peritek VCH-Q, 512×512 resolution). The fixation spot subtended 0.3° of visual angle, and the target stimuli subtended from 0.3 – 3° of visual angle, depending on their eccentricity and had a luminance of 10 or 30 cd/m 2 on a 1 cd/m 2 background.

Using operant conditioning with positive reinforcement, monkeys were trained to perform a series of tasks designed to locate each cell's response field, to determine if the cell had visual- or movement-related activity or both, to determine if cells with fixation-related activity conveyed an extraretinal fixation signal or only had foveal visual receptive fields, and to determine the cell's role in saccade cancellation. Once a cell was isolated, the location and extent of the response field was determined. After fixation of a central spot for a variable interval (500–800 ms), a single target was presented at 1 of 6, 8, or 12 positions varying in direction and eccentricity, and the monkeys were rewarded for generating a single saccade to the target and fixating it for 400 ms. Monkeys also performed a memory-guided saccade task to distinguish movement-related from visually evoked activity (Hikosaka and Wurtz 1983). In the memory-guided saccade task, after fixation of a central spot for a variable interval (500–800 ms), the target was flashed either in the cell's response field or in the opposite hemifield for 50–100 ms. The monkey was required to maintain fixation on the central spot for another 500–1000 ms until the fixation spot disappeared. Reward was contingent on the monkey making a saccade to the remembered location of the target only after the fixation spot disappeared. Once the saccade was made, the target reappeared to provide a target for the monkey to fixate.

A gap task (Fischer and Weber 1993) and a fixation spot blink task (Munoz and Wurtz 1993a) were used while recording from some cells with fixation-related activity to distinguish between a foveal visual response and an extraretinal fixation-related response. In the gap task, after fixation of a central spot for a variable interval (500–800 ms), the fixation spot disappeared. After a 250–650 ms delay in which the screen of the video monitor was blank, the target appeared either in the cell's response field or in the opposite hemifield. Reward was contingent on the monkey making a saccade to the peripheral target. In the fixation-blink task, after fixation of a central spot, the fixation spot was turned off for 550 ms, and the monkey was required to maintain the same gaze angle. After this 550-ms delay, the fixation spot reappeared, and the monkey was required to maintain fixation on the central spot for another 700 ms to receive a juice reward.

The countermanding task provided the main experimental data for this report (Hanes and Schall 1995). All trials during the countermanding task began with the presentation of a central fixation spot (Fig. 1). After fixation of this spot for a variable interval (500–800 ms), a target appeared at one of two locations, either in the most sensitive zone of the cell's response field or 180° in the opposite hemifield at the same eccentricity. Simultaneously, the fixation spot disappeared, instructing the monkey to generate a saccade to the target. On 25, 33, or 50% of the trials after a delay, referred to as the stop-signal delay, the fixation spot reappeared, instructing the monkey to inhibit movement initiation. During the trials in which the stop signal was not presented, monkeys were rewarded for generating a single saccade to the peripheral target within 700 ms and by maintaining fixation on the target for 400 ms. In earlier work, these control trials were referred to as "no signal" trials (Hanes and Schall 1995; Logan and Cowan 1984); in this paper, we will use the designation "no-stop-signal" trials. During trials in which the stop signal was presented, monkeys were rewarded for maintaining fixation on the central spot for 700 ms after the target appeared. In earlier work these trials were referred to as "signal inhibit" trials (Hanes

Trials with no stop signal



Trials with a stop signal

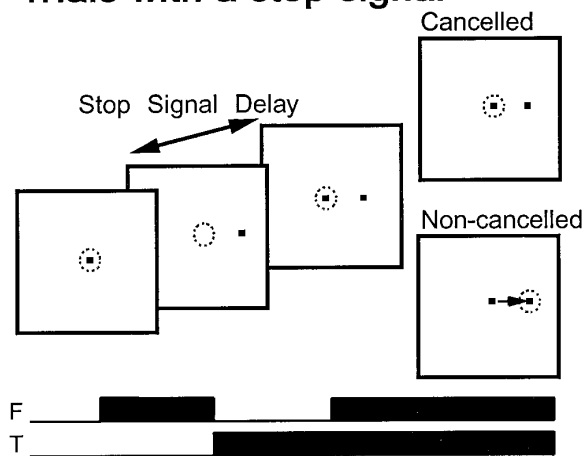


FIG. 1. Trial displays for the countermanding task. Dotted circle indicates the focus of gaze at each interval; arrow, the saccade. All trials began with the presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared. Simultaneously, a target appeared either in the cell's response field or in the opposite hemifield. On a fraction of trials after a delay, referred to as the stop-signal delay, the fixation spot reappeared, instructing the monkey to withhold movement initiation (stop-signal trials). During the trials in which the stop signal was not presented (no-stop-signal trials), monkeys were rewarded for generating a single saccade to the peripheral target. During stop-signal trials, monkeys were rewarded for maintaining fixation on the central spot for 700 ms (cancelled trials). If the monkeys did generate a saccade to the peripheral target during stop-signal trials, no reward was given (noncancelled trials).

and Schall 1995; Logan and Cowan 1984); in this paper, we will use the designation "cancelled" trials because in these trials, monkeys successfully cancelled the planned movement. If the monkeys generated a saccade to the peripheral target during stop-signal trials, no reward was given. In earlier work, these trials were referred to as "signal respond" trials (Hanes and Schall 1995; Logan and Cowan 1984); in this paper, we will use the designation "noncancelled" trials because in these trials, monkeys failed to cancel the planned movement.

Four stop-signal delays ranging from 25 to 275 ms were used. Stop-signal delays were varied according to the monkeys' performance so that at the shortest stop-signal delay, monkeys generally inhibited the movement in >85% of the stop-signal trials and at the longest delay, monkeys inhibited the movement in <15% of the stop-signal trials. The four stop-signal delays were not varied while recording from an individual cell. By adjusting the percentage of stop-signal trials relative to no-stop-signal trials based on

behavioral performance and by maintaining a maximum permissible saccade latency of 700 ms on no-stop-signal trials, we ensured that the monkeys made a speeded response to the presentation of the target and did not adopt the strategy of postponing the saccade until they could determine if the stop signal was going to occur. The 700-ms deadline did not truncate the distribution of reaction times. Also, by imposing a 500-ms time out period after noncancelled trials, we believe that the monkeys were not biased toward generating or withholding a saccade.

Data analysis

The analyses prescribed by the race model of the countermanding paradigm will be described later. The analyses were based on particular treatments of the behavioral and spike data. Inhibition functions were constructed that plot the probability of noncancelled trials as a function of stop-signal delay. To derive reliable parameter estimates, the data were fit with a cumulative Weibull function of the form

$$W(t) = \gamma - (\gamma - \delta) \cdot \exp(-(t/\alpha)^\beta)$$

where t is time after target presentation, α is the time at which the inhibition function reaches 64% of its full growth, β is the slope, γ is the maximum value of the inhibition function, and δ was the minimum value of the inhibition function. The values of γ approached 1.0 but sometimes were as low as 0.6. The values of δ were usually close to 0.0 but sometimes ranged as high as 0.2. The Weibull function fits generally had R^2 of ≥ 0.9 .

Spike density functions were constructed by convolving spike trains with a combination of growth and decay exponential functions that resembled a postsynaptic potential given by the equation

$$R(t) = (1 - \exp(-t/\tau_g)) \cdot (\exp(-t/\tau_d))$$

where rate as a function of time [$R(t)$] varies according to τ_g , the time constant for the growth phase, and τ_d , the time constant for the decay phase. Physiological data from excitatory synapses indicate that 1 and 20 ms are good values for τ_g and τ_d , respectively (Kim and Connors 1993; Mason et al. 1991; Sayer et al. 1990; Thomson et al. 1993). The rationale for this approach has been described previously (Hanes and Schall 1996; Thompson et al. 1996); its motivation was to derive physiologically plausible spike density functions.

RESULTS

Behavioral data analysis

The data obtained in the countermanding task are the inhibition function (Fig. 2A) and the distribution of reaction times in no-stop-signal trials (Fig. 2C). The inhibition function plots the probability of the monkey generating a saccade to the target (noncancelled trials) as a function of stop-signal delay. The inhibition functions show that after short stop-signal delays, the monkeys successfully withheld saccades to the target. But as the stop-signal delay increased, the monkeys increasingly failed to withhold the saccade. Note that the probability of noncancelled trials is equal to 1.0 minus the probability of cancelled trials.

A critical value used in this investigation was the length of time that was required to cancel the saccade being programmed. This duration, known as the *stop-signal reaction time* (SSRT), is a measure that is not directly available in the behavioral data. However, the application of a race model provides a means of estimating the duration of this covert inhibitory process (Logan 1994; Logan and Cowan 1984).

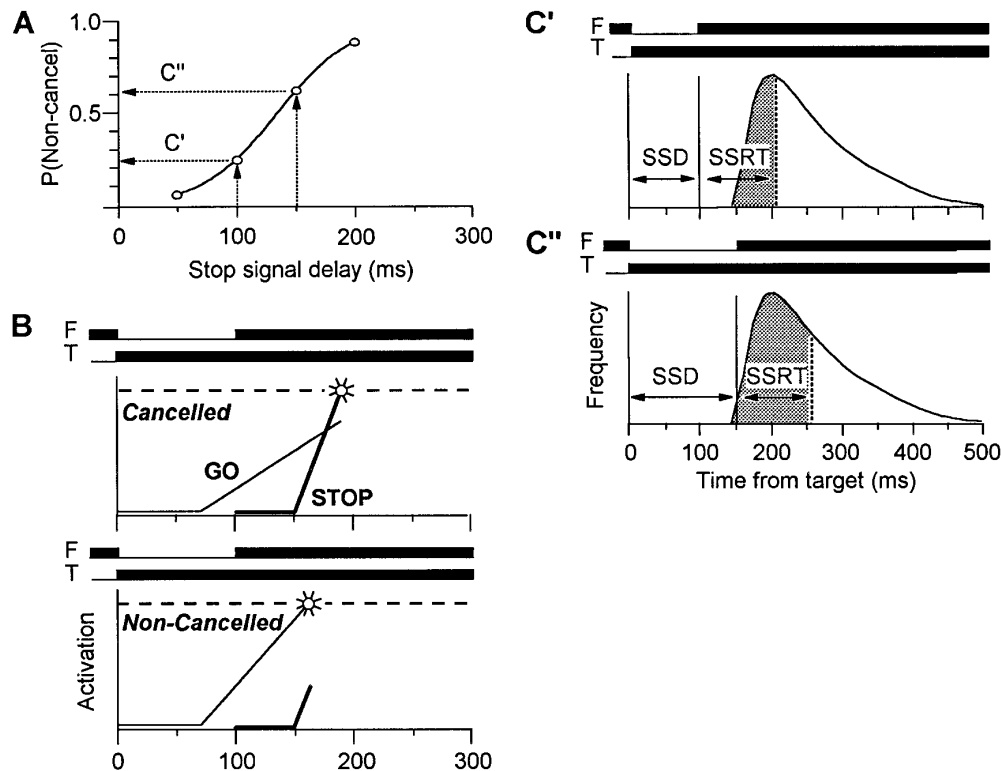


FIG. 2. Countermanding task data and the method for calculating the stop-signal reaction time based on the race model. *A*: inhibition function plots the proportion of stop-signal trials in which the monkey generated a saccade to the target (noncancelled trials) as a function of stop-signal delay. Probability of the saccade escaping the STOP process increased as stop signal delay increased. *B*: 2 possible outcomes of the race model. Temporal sequence of stimulus presentation is indicated (F, central fixation spot; T, peripheral target). Race model consists of a GO process (—) and a STOP process (—) that are racing independently toward their respective thresholds (---). Thresholds for the GO and STOP processes coincide only for ease of illustration. In no-stop-signal trials, only the GO process is active, and a movement is generated when the GO process finishes. In stop signal trials, the STOP process is evoked after the GO process has begun. If the STOP process finishes before the GO process, then the saccade is not generated (cancelled trials). If, on the other hand, the GO process finishes before the STOP process, then a saccade will be generated (noncancelled trials). Figure is drawn to incorporate realistic visual latencies and growth rates. *C*: illustration of the predictions of the race model with a shorter (C') and a longer (C'') stop-signal delay. Timing of the 2 stop-signal delays is superimposed on the distribution of the saccade latencies from no-stop-signal trials. Distribution of saccade latencies during no-stop-signal trials is the range of finish times for the GO process. Comparison of the plots in C' and C'' indicates how the probability of making the movement despite the stop signal, P (noncancelled), changes as a function of stop-signal delay. In C' and C'' , the vertical dotted line indicates the finish time of the STOP process which is equal to the stop-signal delay (SSD) plus the stop-signal reaction time (SSRT). Fraction of the distribution signified by the shading corresponds to the proportion of noncancelled trials at the 2 stop-signal delays. Fraction of the distribution signified by the open area corresponds to the proportion of cancelled trials at the 2 stop-signal delays.

The model consists of a race between a GO process and a STOP process (Fig. 2*B*). The GO process prepares and generates the movement after the presentation of the target. In the oculomotor task, this process includes programming the metrics and initiating the saccade. When the stop signal is not given, only the GO process is active (no-stop-signal trials). Thus the distribution of saccade latencies obtained in no-stop-signal trials is the distribution of finish times of the GO process. If the stop signal is given, then while the GO process proceeds, the STOP process is invoked. As shown in Fig. 2*B*, if the STOP process finishes before the GO process, then the saccade will not be produced, resulting in a cancelled trial. Alternatively, if the GO process finishes before the STOP process, then the saccade will be generated, resulting in a noncancelled trial.

The increasing inhibition function (Fig. 2*A*) arises because increasing the stop-signal delay postpones the onset

of the STOP process, thus increasing the probability that the GO process will finish before the STOP process finishes. This can be seen in Fig. 2*C*, which shows the timing of stop-signal trials with shorter and longer stop signal delays superimposed on the no-stop-signal reaction time distribution. After the shorter stop signal delay (Fig. 2*C'*), the STOP process finishes more often before the GO process, resulting in a lower fraction of noncancelled trials (indicated by the shaded portion of the reaction time distribution). After a longer stop signal delay (Fig. 2*C''*), the STOP process finishes less often before the GO process, resulting in a higher fraction of noncancelled trials.

An analysis of these data based on the race model was done to estimate the SSRT from the behavioral data collected while recording from each cell. Two methods of estimation were used; detailed descriptions of these methods have appeared previously (Hanes and Schall 1995; Logan 1994). It

should be noted that these methods are related closely to analyses performed previously on data from double-step saccade tasks (Becker and Jürgens 1979; Lisberger et al. 1975).

The first method of estimating the SSRT assumes that it is a random variable. Logan and Cowan (1984) showed that the mean SSRT is equal to the difference between the mean reaction time during no-stop-signal trials and the mean value of the inhibition function. The mean of the inhibition function was determined by treating the inhibition function as a cumulative distribution and converting it to a probability density function. If the inhibition function ranges from a probability of 0–1, then the mean is the difference between the probability of responding at the i th stop signal delay minus the probability of responding at the $i - 1$ th stop signal delay multiplied by the i th stop signal delay, summed over all stop signal delays (Logan and Cowan 1984)

Mean of inhibition function

$$= \sum [(\text{Prob}(\text{noncancel})_i - \text{Prob}(\text{noncancel})_{i-1}) \cdot \text{SSD}_i]$$

The actual inhibition functions often had a minimum >0 or a maximum of <1 . To account for this, the mean of the inhibition function was rescaled to reflect the range of the probability of responding. This was accomplished by dividing the mean of the inhibition function by the difference between the maximum and the minimum probabilities of responding

Mean of inhibition function

$$= \frac{\sum [(\text{Prob}(\text{noncancel})_i - \text{Prob}(\text{noncancel})_{i-1}) \cdot \text{SSD}_i]}{(\text{Prob}(\text{noncancel})_{\max} - \text{Prob}(\text{noncancel})_{\min})}$$

Because we used only four stop signal delays to collect a sufficient yield of physiological data, we found that this procedure resulted in inconsistent estimates because of random variability in the form of the inhibition function. To provide an estimate that was less sensitive to this random variability, we fit a Weibull function, $W(t)$, to the inhibition data points (METHODS). An estimate of the mean of the best-fit inhibition function was given by

$$\text{Mean of inhibition function} = \frac{\sum [(W(t) - W(t-1)) \cdot t]}{(W(t_{\max}) - W(t_{\min}))}$$

where t ranges from the minimum to the maximum stop signal delay in 1-ms intervals.

A second method of calculating the SSRT provides an estimate at each stop-signal delay by making the convenient but nonessential assumption that the SSRT is constant. Although this assumption seems unwarranted because it is implausible that a physiological process would take a constant amount of time to execute, its violation does not substantially change the outcome of this analysis (Band 1997; DeJong et al. 1990; Logan and Cowan 1984). By this method, the SSRT is estimated by integrating the no-stop-signal saccade latency distribution, beginning at the time of target presentation, until the integral equals the proportion of noncancelled trials at that stop-signal delay (Fig. 2C). The saccade latency at the limit of the integral represents the finish line of the stop process. In other words, that time value represents the longest saccade latency at which the GO process finished before the STOP process inhibited the saccade. Thus the time between the appearance of the stop signal and this finish

line is the SSRT at this stop-signal delay. In practice, the SSRT is determined by rank ordering the no-stop-signal saccade latencies. The i th saccade latency then is chosen, where i is determined by multiplying the probability of a noncancelled trial at a given stop-signal delay times the total number of no-stop-signal trials. The SSRT is the difference between the i th saccade latency and the stop-signal delay.

The SSRTs estimated using the mean of the inhibition function and by integrating the no-stop-signal saccade latency distribution can vary depending on the shape of the no-stop-signal reaction time distribution and the shape of the inhibition function (see DISCUSSION). The average (\pm SE) SSRT using the mean of the inhibition function was 97.8 ± 2.5 ms for *monkey A* and was 118.0 ± 4.2 ms for *monkey C*. The average SSRT estimated using the method of integration was 87.2 ± 1.6 ms for *monkey A* and was 94.6 ± 2.3 ms for *monkey C*. There is, however, no a priori reason to weight one method of estimation over the other (Band 1996). Therefore, we obtained an overall estimate of SSRT from the behavioral data collected during the physiological recordings from each cell by averaging the SSRT estimates derived from both methods. Figure 3 shows the distribution of estimated SSRTs while recording from all of the cells from two monkeys. Each estimated SSRT plotted in Fig. 3 is the average of the SSRT using both methods of estimation described above. The distribution of averaged SSRTs was unimodal and spanned <80 ms. Across both monkeys that provided physiological data during the countermanding task the average (\pm SE), SSRT was 97 ± 1.2 ms. The average SSRT for *monkey A* was 93 ± 1.5 ms and for *monkey C* was 103 ± 1.9 ms. For comparison, the average SSRT for *monkey B*, which provided some of the fixation-related cells, was 84 ms as reported previously (Hanes and Schall 1995).

Cell classification

A total of 113 cells were collected from four hemispheres in three monkeys that exhibited task-related activity and provided sufficient data in the necessary trial conditions to be included in this report. The memory-guided saccade task was used to classify neurons according to the criteria of

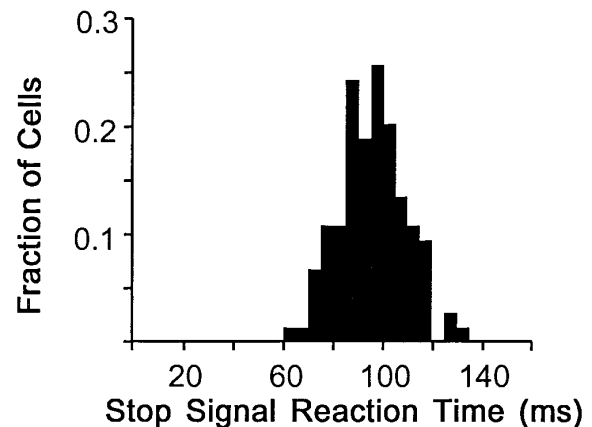


FIG. 3. Distribution of stop-signal reaction times estimated from the behavioral performance while recording from all frontal eye field (FEF) cells.

Bruce and Goldberg (1985). Examples of the four cell types recorded in the FEF for this study are shown in Fig. 4. Cells with visually evoked activity began to discharge after the presentation of a peripheral visual target and had no elevation in activity before a memory-guided saccade. Two types of cells with visually evoked activity have been described previously in the memory-guided saccade task (Bruce and Goldberg 1985). Phasic visual cells discharged a brief burst of activity after the presentation of the peripheral target but were inactive during the delay period and before the saccade (Fig. 4A). In contrast, tonic visual cells discharged a burst of activity after target presentation followed by a lower, maintained discharge rate that persisted through the delay period and the saccade (Fig. 4B). A total of 48 cells with visually evoked activity were analyzed for this report.

Cells with movement-related activity were defined as cells that exhibited an increased discharge rate before a memory-guided saccade (Fig. 4C). These cells may or may not exhibit a visual response. Previously, cells with movement-related activity have been separated into two groups. Cells with both visual- and movement-related activity would be referred to as visuomovement cells and cells with only movement-related activity would be referred to as movement cells (Bruce and Goldberg 1985). For this report, both movement and visuomovement cells will be referred to as cells with movement-related activity. A total of 51 cells with movement-related activity were analyzed.

Cells with fixation-related activity were defined by an increased firing rate after fixation of the central spot and by a pause in their rate of discharge before and during the saccade (Fig. 4D). Before the appearance of the fixation spot, these cells fired sporadically. The fixation-related cells we recorded fulfilled several other criteria, besides a sustained level of activity during fixation, that help define fixation cells in the superior colliculus (Munoz and Wurtz 1993a). All fixation-related cells we recorded in FEF paused before saccades in all directions, and most were reactivated after saccade termination. In addition, when the fixation spot was removed momentarily and the monkey was required to maintain the same gaze angle, there was a reduction in the discharge rate. However, the cells tested in this way continued to fire above the baseline level during the period when the fixation spot was not present (Fig. 8B). A total of 14 fixation-related cells were recorded for this report. Of these cells, seven were collected during the countermanding task. Although this is a limited sample, fixation-related cells were found in all three monkeys and discharged in a manner similar to fixation cells in the superior colliculus.

The location of task-related cells in *monkeys A and C* have not been localized histologically because physiological recordings are continuing in these animals. However, the electrode penetrations advanced through the rostral bank of the arcuate sulcus as identified by the sulcal pattern observed at the time of the craniotomy and by the incidence of visual and saccade-related activity. The location of FEF also was confirmed by the depths of the cells. Physiological findings did not differ across monkeys.

Determination of a cancellation signal

To determine if a cell was involved in canceling a planned saccade, we needed to compare the activity of cells in trials

in which saccade initiation was inhibited (cancelled trials) and trials in which a saccade was initiated (no-stop-signal trials). In cancelled trials, saccade initiation was inhibited because the STOP process finished before the GO process finished. Thus a valid comparison with the cancelled trials is only those no-stop-signal trials in which saccade initiation *would* have been inhibited if the stop signal had occurred. In other words, these are the no-stop-signal trials in which the GO process was slow enough that the STOP process would have finished before the GO process if the stop signal had been presented. This subset of no-stop-signal trials, which hereafter will be referred to as *latency-matched* no-stop-signal trials, are indicated by the open region of the no-stop-signal saccade latency distribution shown in Fig. 2C. In practice, these *latency-matched* no-stop-signal trials are the no-stop-signal trials with saccade latencies greater than the stop-signal delay plus the duration of the STOP process, i.e., the SSRT.

To influence behavior, a cell must discharge differently during cancelled trials than during latency-matched no-stop-signal trials. Furthermore, because the SSRT estimates when the preparation of the saccade was cancelled, the differential activity must occur at or before the SSRT for the cell to be involved directly in canceling the saccade. We used two analyses to quantify the magnitude and time course of the differential activity during cancelled and latency-matched no-stop-signal trials. First, a *t*-test was applied to the spike count in the 40-ms interval beginning 20 ms before the estimated SSRT in cancelled and latency-matched no-stop-signal trials. This was done to allow for small errors in the estimation of SSRT. A significant difference in the spike count in the interval around the estimated SSRT was regarded as evidence for a saccade cancellation signal. Second, the average spike density functions in cancelled and latency-matched no-stop-signal trials were compared as a function of time from target presentation. This was done to provide a complementary estimate of whether and when neural activity distinguished saccade inhibition from saccade initiation. To perform this time-course analysis, we subtracted the average spike density function for cancelled trials from the average spike density function during latency-matched no-stop-signal trials. This subtraction was performed for cells with visually evoked activity and for cells with movement-related activity. Because of their opposite sign of modulation, for cells with fixation-related activity, we subtracted the average spike density function for latency-matched no-stop-signal trials from the average spike density function during cancelled trials. The resulting spike density functions will be referred to as differential spike density functions. An example of a differential spike density function is shown in Fig. 5. The time at which significant differential activity began during cancelled and latency-matched no-stop-signal trials was defined as the instant when the differential spike density function exceeded by 2 SD the mean difference in activity during the 600-ms interval before target presentation, provided the difference reached 6 SD and remained >2 SD threshold for 50 ms. The time interval between the defined onset of differential activity and the SSRT then was determined. If the time when the differential activity arose was earlier than or equal to the SSRT, we regarded this as posi-

tive evidence for a cancellation signal. We will refer to this time difference as the *cancellation time*.

Figure 5 shows the activity of a representative cell with movement-related activity collected during the countermanding task with 100- and 183-ms stop-signal delays. This cell illustrates one of the major findings of this report. Figure 5, *top two panels*, shows the activity in no-stop-signal trials that are latency-matched to cancelled trials. The activity during these trials began ~80 ms after target presentation and continued to rise until saccade initiation. Figure 5, *middle two panels*, shows the activity during the cancelled trials. Similar to the latency-matched no-stop-signal trials, the ac-

tivity began to increase ~80 ms after target presentation but then began to decrease ~170 ms after target presentation for the 100-ms stop-signal delay and ~260 ms after target presentation for the 183-ms stop-signal delay. Figure 5, *bottom two panels*, the spike density functions for cancelled and latency-matched no-stop-signal trials are superimposed. The estimated SSRT while this cell was recorded was 95 ms. For the 100-ms stop-signal delay, the discharge rate in the 40-ms interval around the SSRT was significantly less in cancelled trials, 45.2 Hz, than in latency-matched no-stop-signal trials, 69.6 Hz ($t = 2.75$; $df = 102$; $P < 0.05$). For the 183-ms stop-signal delay, the discharge rate in the 40-ms interval around the SSRT was also significantly less in cancelled trials, 34.2 Hz, than in latency-matched no-stop-signal trials, 112.7 Hz ($t = 6.24$; $df = 80$; $P < 0.05$).

This result shows that the level of neural activity was significantly less in cancelled than in latency-matched no-stop-signal trials around the time of the SSRT. However, for these cells to directly influence saccade cancellation, the difference in activity must occur at or before the SSRT. As indicated by the vertical arrow in Fig. 5, differential activity during cancelled and latency-matched no-stop-signal trials arose 5 and 6 ms before the SSRT for the 100- and 183-ms stop-signal delays, respectively. Because the difference in activity occurred within the SSRT, the activity of this cell is sufficient to be involved directly in canceling the saccade that was being programmed.

A ratio of the discharge rate in the 40 ms surrounding the SSRT during latency-matched no-stop signal and cancelled trials was determined for each stop-signal delay collected with each cell with movement-related activity. Figure 6A shows the distribution of these ratios. Ninety-two percent of the movement-related cells had a significant ratio in at least one stop-signal delay (t -test, $P < 0.05$). Overall, 97% of the stop-signal delays from all movement-related cells had ratios >1.0 . For the groups of trials that had significant ratios, the average ratio was 2.84 ± 0.24 which was significantly >1.0 ($t = 7.76$; $df = 101$; $P < 0.05$). For the groups of trials that had nonsignificant ratios, the average ratio was 1.36 ± 0.78 , which was also significantly >1.0 ($t = 4.59$; $df = 36$; $P < 0.05$). Thus, for almost all cells with movement-related activity, the discharge rate around the time of

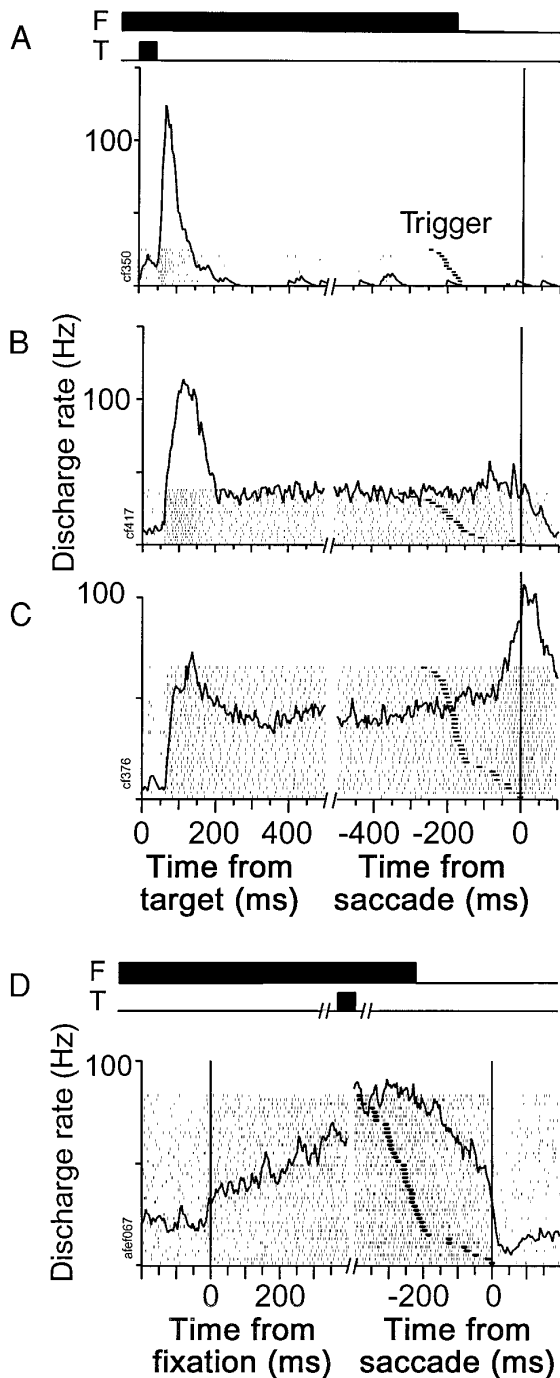


FIG. 4. Four types of FEF cells distinguished during the memory-guided saccade task. Temporal sequences of stimulus presentation are indicated (F, central fixation spot; T, peripheral target). Neural activity is illustrated in a raster display with superimposed average spike density functions. Each row of rasters indicates 1 trial. Each vertical tickmark indicates 1 action potential. Horizontal tickmarks indicate the time that the fixation spot disappeared signaling the monkey to generate a saccade to the remembered location of the target. Trials are sorted by reaction time. A–C, *left*: aligned on target presentation; *right*: aligned on saccade initiation. Spike density function in D is aligned on the time the monkey fixated the central fixation spot (*left*) and on saccade initiation (*right*). A: a phasic visual cell that exhibited a brief burst of activity after the presentation of a peripheral target in its response field. B: a tonic visual cell that discharged a burst of activity after the presentation of a target in its response field followed by a lower, maintained rate of discharge that continued through the delay period until the memory-guided saccade. C: a cell with movement-related activity that exhibited an elevation in discharge rate associated with a memory-guided saccade. D: a cell with fixation-related activity that began to discharge after the monkey fixated the central fixation spot and paused before saccade initiation.

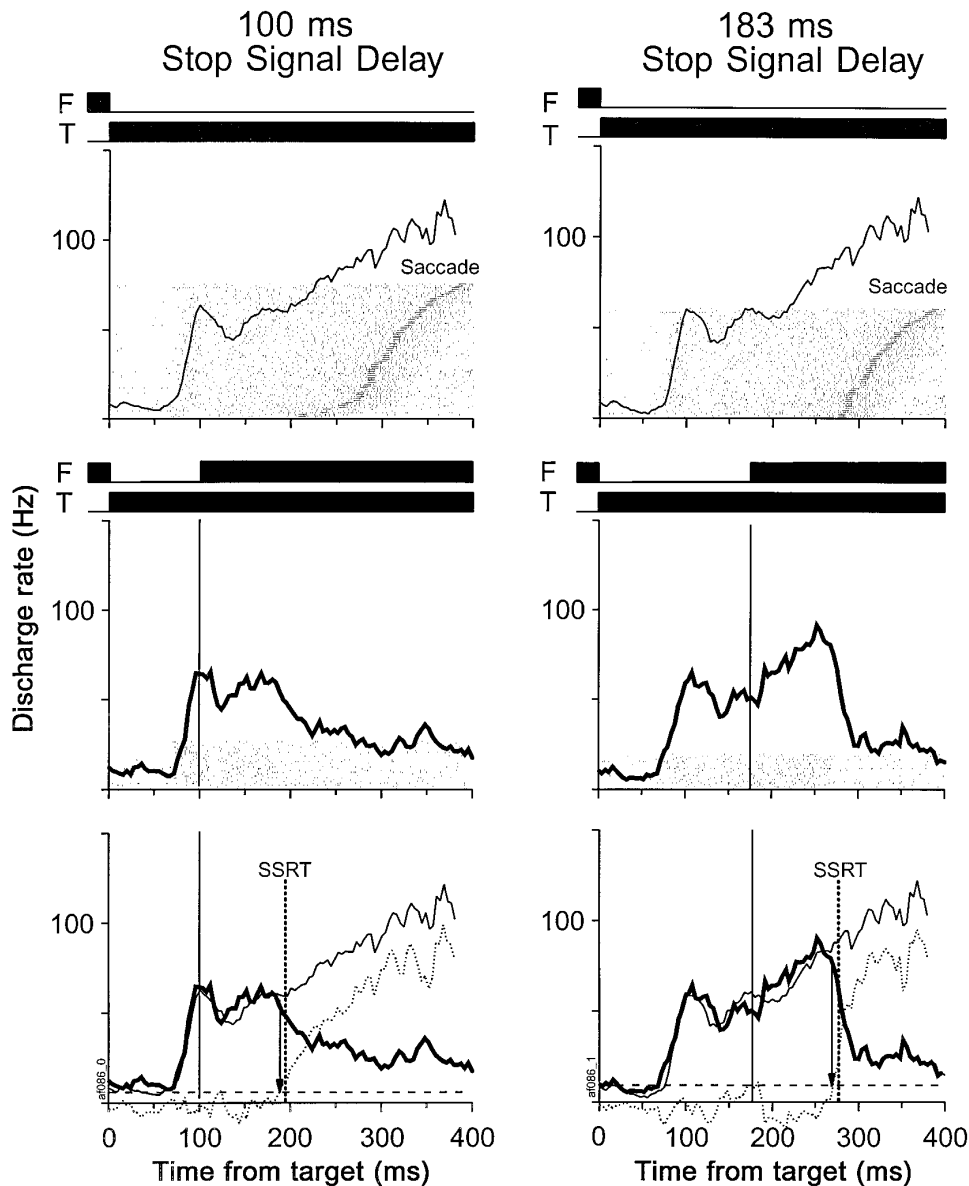


FIG. 5. Activity of a representative cell with movement-related activity aligned on the time of target presentation. Trials collected during the countermanning task with stop-signal delays of 100 ms (left) and 183 ms (right) are shown. No-stop-signal trials that are latency matched to cancelled trials are shown (top 2 panels). Cancelled trials also are shown (middle 2 panels). Conventions as in Fig. 4, except the horizontal tickmarks in the top panels indicate the time of saccade initiation. Spike density functions for cancelled (—) and latency-matched no-stop-signal trials (—) are shown. Bottom 2 panels: comparison of the spike density functions during cancelled and latency-matched no-stop-signal trials. ···, differential spike density function. |, time of presentation of the stop-signal; †, estimated SSRT; — — —, discharge rate 2 SD above the mean of the differential spike density function rate in the interval of fixation 600 ms before the presentation of the target; ‡, time at which the differential activity became significant.

the SSRT was significantly less in cancelled trials than in latency-matched no-stop-signal trials.

We refer to the time relative to the SSRT at which the differential activity began as the cancellation time. Figure 6B shows the distribution of cancellation times for each stop-signal delay collected with each cell. These times were calculated using the SSRT estimated from the behavioral data collected while each cell was recorded. A cancellation time occurred in at least one stop-signal delay in 86% of the FEF movement-related neurons. Overall, 58% of the groups had cancellation times that occurred before the SSRT. The average cancellation time for all cells with movement-related activity was 1.1 ± 2.6 ms before the SSRT. For cells exhibiting significantly less activity around the SSRT in cancelled trials as compared with no-stop-signal trials, the average cancellation time was 8.5 ± 2.6 ms before the SSRT.

As mentioned above, the estimate of SSRT is potentially unreliable with data sets of <100–150 no-stop-signal trials.

Therefore we repeated the analysis comparing the time at which the activity decayed in cancelled trials for each cell to the SSRT averaged across all the recording sessions for each monkey. According to this approach, the average cancellation time was 1.50 ± 2.53 ms before the grand average SSRT. For cells exhibiting significantly less activity around the SSRT in cancelled trials as compared with no-stop-signal trials, the average cancellation time was 7.19 ± 2.68 ms before the grand average SSRT. Hence, measuring the cancellation time relative to the SSRT estimated from data collected while each cell was recorded or relative to the average of all SSRTs yielded similar results. The fact that most cells with movement activity had cancellation times before or coincident with the SSRT is evidence that these cells generate a signal sufficient to cancel the impending saccade.

Independence of the GO and STOP processes

A central premise of the race model used to estimate the SSRT is that the GO and STOP processes are stochastically

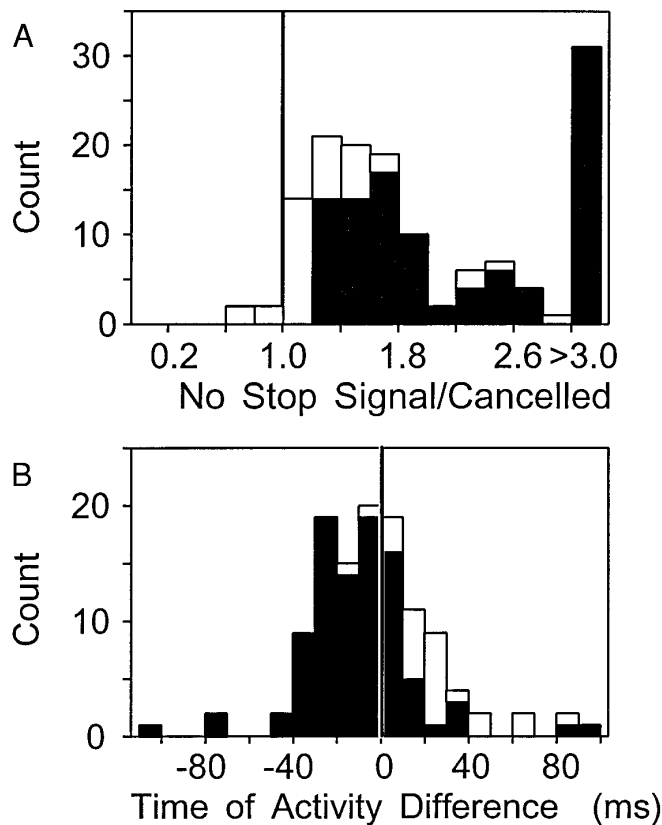


FIG. 6. *A*: distribution of the ratios of activity in the 40-ms interval around the SSRT in latency-matched no-stop-signal trials and cancelled trials for the group of trials collected in each stop-signal delay in 51 cells with movement-related activity. Each stop-signal delay from each cell contributed 1 data point. Solid bar, ratios of groups with statistically significant differences. *B*: distribution of the cancellation times, i.e., the time at which the activity during cancelled and latency-matched no-stop-signal trials became different measured relative to the SSRT. Each stop-signal delay from each cell contributed 1 data point. Negative times indicate differences arising before the estimated SSRT. Solid bar, groups of trials that had a significant ratio of the activity in cancelled and latency-matched no-stop-signal trials as indicated in *A*.

independent. Specifically, this means that the finish time of each process is uncorrelated with the finish time of the other process. Violation of this premise is not fatal; it only means that the estimate of the SSRT will vary as a function of stop-signal delay (DeJong et al. 1990; Logan and Cowan 1984). To test directly whether the growth of the STOP process affected the growth of the GO process, neural activity was compared between noncancelled and no-stop-signal trials. In both no-stop-signal and noncancelled trials, a saccade was generated to the peripheral target. However, in noncancelled trials, both the GO and STOP processes are active, whereas in no-stop-signal trials, only the GO process is active. If the STOP process interfered with the GO process, then the rate of growth of movement-related activity before saccades in noncancelled trials should be slower than that observed before saccades in no-stop-signal trials. Similar to the analysis of the cancelled trials, the comparison between noncancelled and no-stop-signal trials is dependent on correctly accounting for saccade latency. In noncancelled trials, the GO process reached its threshold before the STOP process so a saccade was initiated. Thus, a valid comparison

with these noncancelled trials is those no-stop-signal trials in which a saccade would have been initiated even if a stop signal had occurred. In other words, these are the no-stop-signal trials in which the GO process was fast enough that it would have crossed its threshold before the STOP process if a stop signal had occurred. This subset of no-stop-signal trials, referred to as *latency-matched* no-stop-signal trials, are indicated by the shaded region of the no-stop-signal saccade latency distribution shown in Fig. 2C. In practice, these are the no-stop-signal trials with saccade latencies less than the stop-signal delay plus the SSRT.

However, an additional restriction must be applied to this analysis. To test the independence premise, we must analyze trials in which both the GO and STOP processes are active. The comparison would not be valid for the noncancelled trials with the shortest saccade latencies because the saccade may have been initiated before the stop signal was even presented. Further, once the stop signal had been presented, a visual-response latency must elapse before cells in the FEF can register that the stop signal occurred. Therefore, both the GO and STOP processes would be active only in noncancelled trials with saccade latencies greater than the stop-signal delay plus a visual-response latency. To provide a valid comparison, this minimum saccade latency restriction also was applied to the latency-matched no-stop-signal trials. A 50-ms value for the visual-response latency was chosen as trade-off between the need to have a suitably long latency and the need to preserve enough trials for statistical power. Thus to test the independence premise, we compared the movement-related activity in a subset of noncancelled trials with a subset of latency-matched no-stop-signal trials. Trials with latencies less than the stop signal delay plus 50 ms were excluded from this comparison.

It is worth noting that, as described above there are two types of latency-matched no-stop-signal trials. No-stop-signal trials can be latency matched to cancelled and to noncancelled trials. No-stop-signal trials that are latency matched to cancelled trials are those no-stop-signal trials with saccade latencies that are long enough (i.e., greater than the stop-signal delay plus the SSRT) that they would have been inhibited if a stop signal had been presented. No-stop-signal trials that are latency matched to noncancelled trials are no-stop-signal trials with saccade latencies that are short enough (i.e., less than the stop-signal delay plus the SSRT) that they still would have been generated even if a stop signal had been presented.

Two analyses were conducted with the physiological data to test the independence of the GO and the STOP processes. First, a *t*-test was applied to the spike count in noncancelled and latency-matched no-stop-signal trials. For cells with movement-related activity, the spike count was measured in the 40-ms interval before saccade initiation during each trial. A significant difference in the spike count was regarded as evidence against the independence of the GO and STOP processes. Second, the average spike density functions in noncancelled and latency-matched no-stop-signal trials were compared as a function of time from target presentation using a differential spike density function. The time that the differential activity began was determined as described above.

Figure 7, *A* and *B*, shows the activity of a cell with move-

ment-related activity during the designated noncancelled and latency-matched no-stop-signal trials. Data for this cell also were shown in Fig. 5. During both noncancelled and latency-matched no-stop-signal trials, the activity began to increase ~80 ms after target presentation and continued to grow until it peaked shortly after saccade initiation. The activity during the selected noncancelled and latency-matched no-stop-signal trials was not significantly different (*t*-test, $P > 0.05$). The discharge rate in the 40-ms interval before saccade initiation was 117.1 Hz during noncancelled trials and 128.0 Hz during latency-matched no-stop-signal trials. The differential spike density function was never significantly different from baseline levels.

A ratio of the discharge rate during noncancelled and latency-matched no-stop-signal trials was determined for each stop-signal delay in which sufficient trials were collected with each cell. Figure 7C shows a distribution of these ratios for all cells with movement-related activity. Only one cell had a significant ratio in one stop-signal delay. The average ratio was 1.01 ± 0.02 , which was not significantly different from 1.0 (*t*-test, $P > 0.1$). In addition, for all the cells with movement-related activity, the time course of activity analyzed using the differential spike density function was not significantly different in noncancelled and latency-matched no-stop-signal trials (*t*-test, $P > 0.1$). This result indicates that the STOP process does not influence the growth of the GO process.

Fixation-related activity

Recent investigations of the superior colliculus have demonstrated the existence and functional role of fixation cells (Munoz and Wurtz 1993a,b). Evidence has indicated that similar neurons exist in FEF (Bizzi 1968; Bruce and Goldberg 1985; Segraves 1992; Segraves and Goldberg 1987) but the functional properties of these neurons have not been characterized. Because fixation cells convey such a key signal to control gaze, we made particular efforts to locate and record from them. Data were collected from a sample of neurons that had foveal receptive fields and apparent fixation signals. The locations of seven cells with fixation-related activity recorded in *monkey B* have been localized histologically to ~3-mm lateral of the principle sulcus, in the rostral bank of the arcuate sulcus. The cells with fixation-related activity were recorded at depths of 2–4 mm from the cortical surface in *monkey B*. In recordings from the other two monkeys, we encountered cells with fixation-related activity somewhat more frequently in penetrations in which movement-related activity was associated with short (2–4°)-amplitude saccades than in penetrations in which movement-related activity was associated with longer saccades.

We distinguished visual neurons with foveal receptive fields from neurons that may have a foveal receptive field but also carried an extraretinal fixation signal using previously published tests (Munoz and Wurtz 1993a). Figure 8 shows the activity of a fixation-related cell recorded in FEF during the gap, fixation-blink, and the countermanding tasks. The cell's activity during these tasks indicates that it conveys an extraretinal fixation signal and was not simply a foveal visual cell. During all tasks, the cell began to discharge after fixation of the central spot and paused during the saccade. In

the gap task, the discharge rate decreased from ~90 to ~50 Hz after the central fixation spot was removed (Fig. 8A). The discharge rate of the cell remained ~50 Hz until after the target was presented. Approximately 20 ms before saccade initiation there was a pause in activity. Because the discharge rate during the gap interval remained elevated above the discharge rate during the intertrial interval, the response of this cell could not be due solely to a foveal visual response; instead it seemed to discharge for both a foveal stimulus and active fixation in the absence of a foveal stimulus. This result is consistent with the activity observed during the blink paradigm (Fig. 8B). Before the fixation spot was extinguished and after it reappeared, the discharge rate of the cell was ~70 Hz. During the interval in which fixation spot was not present but the monkey was required to maintain the same gaze angle, the discharge rate fell to ~40 Hz. The discharge rate in the blink interval was still above the discharge rate during the intertrial interval. As with the gap task, this result suggests that the cell fires for both a foveal stimulus and also during active fixation.

Figure 8C shows the activity of this fixation-related cell during the countermanding task. The SSRT while recording from this cell was 111 ms. During cancelled trials, the cell phasically increased its discharge rate followed by a maintained elevation in discharge rate after the presentation of the stop signal. The discharge rate in the 40-ms interval around the SSRT was significantly greater in cancelled trials, 59.7 Hz, than in latency-matched no-stop-signal trials, 22.6 Hz ($t = 3.82$; $df = 101$; $P < 0.05$). Further, the cancellation time, indicated by the vertical arrow in the figure, occurred 14 ms before the SSRT, indicated by the vertical dotted line. This result suggests that this cell could have been involved directly in countermanding the saccade that was being programmed because the difference in activity occurred within the SSRT.

A ratio of the discharge rate in the 40-ms interval around the SSRT during cancelled and latency-matched no-stop-signal trials was determined for each stop-signal delay collected with each fixation cell. Six of seven of the fixation cells had a significant ratio in at least one stop-signal delay (*t*-test, $P < 0.05$). The average ratio for all stop-signal delays from all fixation-related cells was 1.58 ± 0.16 , which was significantly > 1.0 ($t = 3.74$; $df = 20$; $P < 0.05$). Thus for a majority of fixation-related cells, the discharge rate around the time of the SSRT was significantly greater when saccades were inhibited than when saccades were made but could have been inhibited. The time course analysis indicated that a cancellation signal occurred on average 0.22 ± 4.9 ms after the SSRT; this was not significantly different from 0 (*t*-test, $P > 0.05$). Thus for the fixation-related cells we recorded during the countermanding task, the time of the cancellation signal coincides with the time of the SSRT. Furthermore, the fixation cell cancellation times were not significantly different from the cancellation times in cells with movement-related activity (*t*-test, $P > 0.05$).

To determine if the increase in activity that we observed during cancelled trials represents simply a visual response to the foveal stop signal or instead is an extraretinal countermanding signal, we compared the activity during noncancelled and latency-matched no-stop-signal trials (Fig. 8D). In both noncancelled and no-stop-signal trials, the monkeys

generated a saccade to the peripheral target, however, in noncancelled trials, the fixation spot had reappeared instructing the monkeys to inhibit saccade initiation. If the increase in activity during cancelled trials is a countermending signal, then during noncancelled trials, there should not be a significant increase in the discharge rate of the cell.

Two analyses were used. First, a *t*-test was applied to the spike count in noncancelled and latency-matched no-stop-

signal trials. For cells with fixation-related activity, the spike count was measured in the 40-ms interval before saccade initiation during each trial. A significant difference in the spike count was regarded as evidence that the increase in activity during cancelled trials represents a simple foveal response to the presentation of the stop-signal. However, none of these data yielded a statistically significant difference in activity between noncancelled and latency-matched no-stop-signal trials. Also, a ratio of the discharge rate during noncancelled and latency-matched no-stop-signal trials was determined for each stop-signal delay in which sufficient trials were collected with each fixation cell. The average ratio was 0.95 ± 0.12 , which was not significantly different from 1.0 (*t*-test, $P > 0.05$).

In the second analysis, the average spike density functions in noncancelled and latency-matched no-stop-signal trials were compared as a function of time from target presentation using a differential spike density function. The time that the differential activity began then was determined according to the same criteria used for the movement-related activity. For all the cells with fixation-related activity, the time course of activity analyzed using the differential spike density function was not significantly different in noncancelled and latency-matched no-stop-signal trials (*t*-test, $P > 0.05$). This result indicates that the increase in activity during cancelled trials is not a simple foveal visual response but instead is a countermending signal that inhibits saccade initiation.

Visually evoked activity

Figure 9 shows the activity of two cells with visually evoked activity during cancelled and latency-matched no-stop-signal trials for two stop-signal delays. Figure 9, *A* and *B*, shows the activity of a representative visual cell with a phasic burst of activity after target presentation and no movement-related activity. The estimated SSRT while recording from this cell was 116 ms. The activity around the SSRT was not different during cancelled and latency-matched no-stop-signal trials for either the 68-ms (Fig. 9*A*) or the 168-ms (Fig. 9*B*) stop-signal delay (*t*-test, $P > 0.05$). The differential spike density function was never significantly different from the baseline level. Figure 9, *C* and *D*, shows the activity of a tonic visual cell during cancelled and latency-matched no-stop-signal trials for two stop-signal delays. This cell began to discharge ~ 60 ms after target presentation and continued to discharge at a maintained firing rate through the saccade. The SSRT estimated while recording from this cell was 101 ms. Like the visual cell shown in Fig. 9, *A* and *B*, the activity around the SSRT was not different during cancelled and latency-matched no-stop-

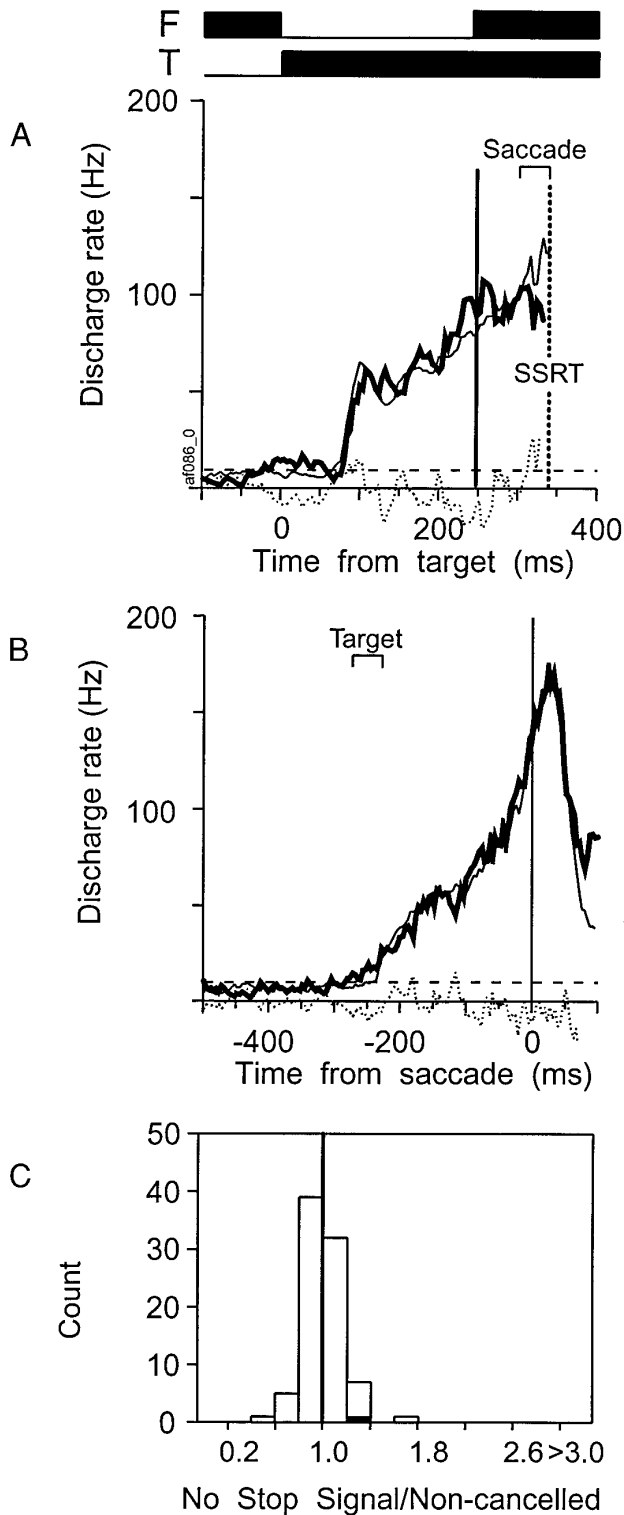


FIG. 7. Comparison of noncancelled and latency-matched no-stop-signal trials. Activity of a cell with movement-related activity is shown aligned on the time of target presentation (*A*) and aligned on saccade initiation (*B*). In *A*, the solid vertical line indicates the time the stop signal was presented, and the dotted vertical line indicates the stop-signal reaction time. Conventions as in Fig. 5, except that the thick solid lines represent the average spike density functions during noncancelled trials and the thin solid lines represent the spike density functions during latency-matched no-stop-signal trials. *C*: distribution of the ratios of activity in the 40-ms interval before saccade initiation in noncancelled and latency-matched no-stop-signal trials. Each stop-signal delay from each cell contributed 1 data point. Solid bars, ratios of groups with statistically significant differences.

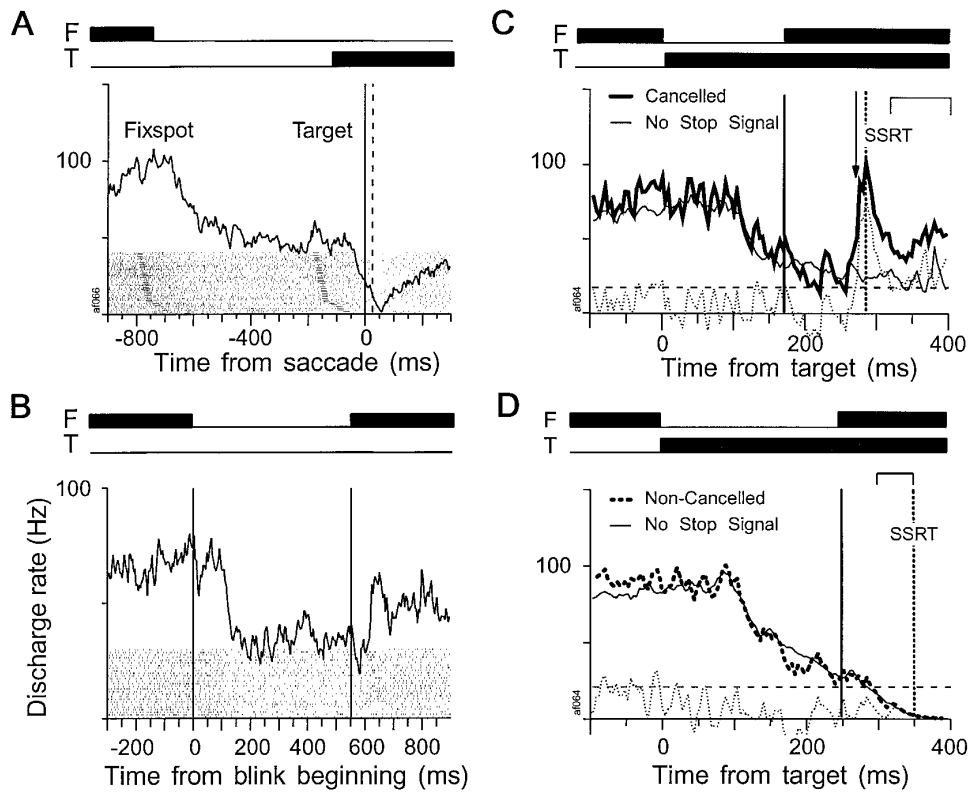


FIG. 8. Fixation-related activity. *A*: activity during a 650-ms gap task. Trials are aligned on saccade initiation (solid vertical line); dashed vertical time shows the average time of saccade termination. *B*: fixation-blink task. Trials are aligned on the disappearance (left vertical line) and on the reappearance (right vertical line) of the fixation spot. *C* and *D*: countermanding task. Trials are aligned on the time of target presentation. Spike density functions are indicated by thin solid lines for no-stop-signal trials, by a thick solid line for cancelled trials (*C*) and by a thick dotted line for noncancelled trials (*D*). Solid vertical line shows when the stop signal was presented. Dotted vertical line shows the stop-signal reaction time (SSRT). Bracket at the top of *C* and *D* indicates the range of saccade latencies contributing to the appropriate latency-matched no-stop-signal trials. Otherwise, conventions as in Fig. 5.

signal trials for either the 68-ms (Fig. 9C) or 168-ms (Fig. 9D) stop-signal delay (t -test, $P > 0.05$). The differential spike density function was never significantly different from the baseline level.

Although most cells having exclusively visually evoked activity exhibited no significant difference in activity before the SSRT, many tonic visual cells, defined using the memory-guided saccade task, did exhibit a differential level of activation in cancelled and latency-matched no-stop-signal trials after the SSRT. Figure 10 shows the activity of a visual cell during trials with a 100-ms stop-signal delay. This cell showed no modulation associated

with memory-guided saccades. The SSRT while recording from this cell was 83 ms. The activity during cancelled and latency-matched no-stop-signal trials was not significantly different in the 40-ms interval around the SSRT ($P > 0.05$). After the SSRT had elapsed, however, the activity of the cell decayed during cancelled trials. This decay occurred even though the target was still in the cell's receptive field and the monkey was still fixating the central fixation spot. The difference in activity between cancelled and no-stop-signal trials became significantly elevated above the difference in the baseline period 80 ms after the SSRT. Because the differential discharge occurred so long

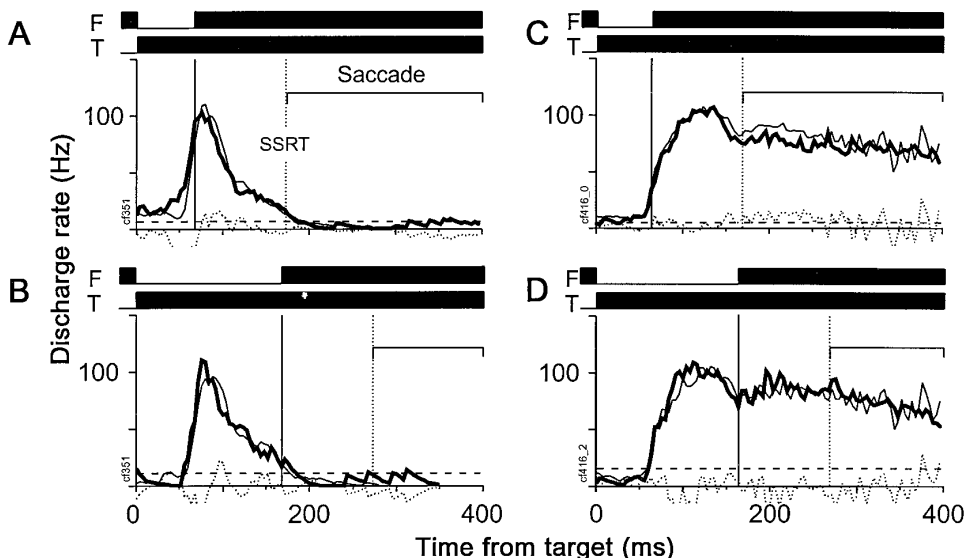


FIG. 9. Average spike density functions of 2 cells with visually evoked activity during cancelled (thick) and latency-matched no-stop-signal trials (thin) aligned on the time of target presentation. *A* and *B*: activity of a representative cell with phasic visually evoked activity during cancelled trials with stop-signal delays of 68 and 168 ms and the latency-matched no-stop-signal trials. *C* and *D*: cell with tonic visually evoked activity during cancelled trials with stop-signal delays of 68 and 168 ms and the latency-matched no-stop-signal trials. Conventions as in Fig. 5 except that the bracket above the average spike density functions indicates the range of saccade latencies during latency-matched no-stop-signal trials.

after the SSRT, this cell could not be directly involved in canceling the impending saccade.

A ratio of the discharge rate in the 40-ms interval around the SSRT during cancelled and latency-matched no-stop-signal trials was determined for each stop-signal delay collected with each visual cell. Figure 11A shows the distribution of these ratios for all 48 visual cells. Ten of the visual cells had a significantly lower discharge rate in cancelled trials than in latency-matched no-stop-signal trials in one stop-signal delay (t -test, $P < 0.05$). For the groups of trials that had significant ratios, the average ratio was 1.49, which was significantly >1.0 ($t = 5.98$; $df = 9$; $P < 0.05$). In these groups of trials, the significant difference in activity around the SSRT occurred because in cancelled trials the cells exhibited reductions in discharge rate after the SSRT. For the groups of trials that had nonsignificant ratios, the average ratio was 1.03, which was not significantly >1.0 (t -test, $P > 0.1$). Thus for a majority of visual cells, the discharge rate around the time of the SSRT was not significantly different in cancelled and latency-matched no-stop-signal trials.

Although the discharge rate around the time of the SSRT was not different in cancelled and latency-matched no-stop-signal trials for most visual cells, some tonic visual cells exhibited a differential response after the SSRT had elapsed. Figure 11B shows the distribution of the times at which the differential spike density function during cancelled and latency-matched no-stop-signal trials became different for each stop-signal delay collected with each cell. A differential level of activation between cancelled and latency-matched no-stop-signal trials arose in at least one stop-signal delay in 50% of the FEF visual neurons but almost always after the movement already had been cancelled. The average time of differential activity for all visual cells was 50.7 ± 7.4 ms after the SSRT. Because visual cells exhibited differential activity after the SSRT, they cannot be directly involved in canceling the planned saccade.

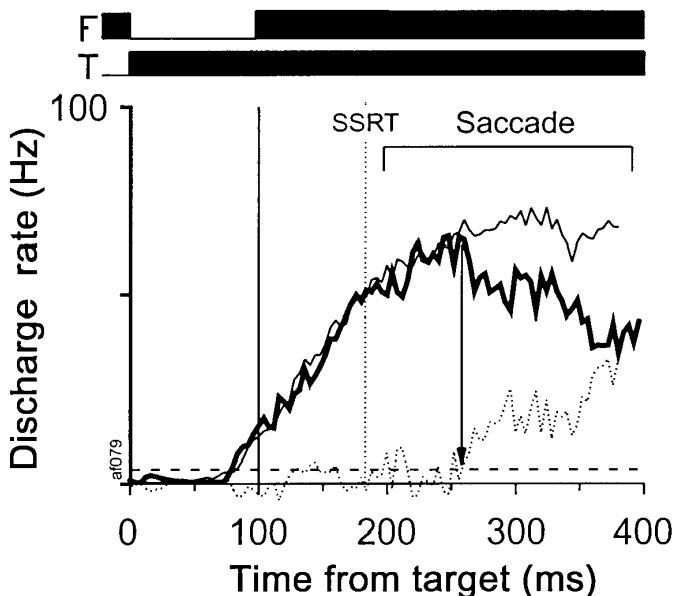


FIG. 10. Activity of a cell with tonic visually evoked activity that exhibited reduced activity during cancelled as compared with latency-matched no-stop-signal trials after the SSRT. Conventions as in Fig. 9.

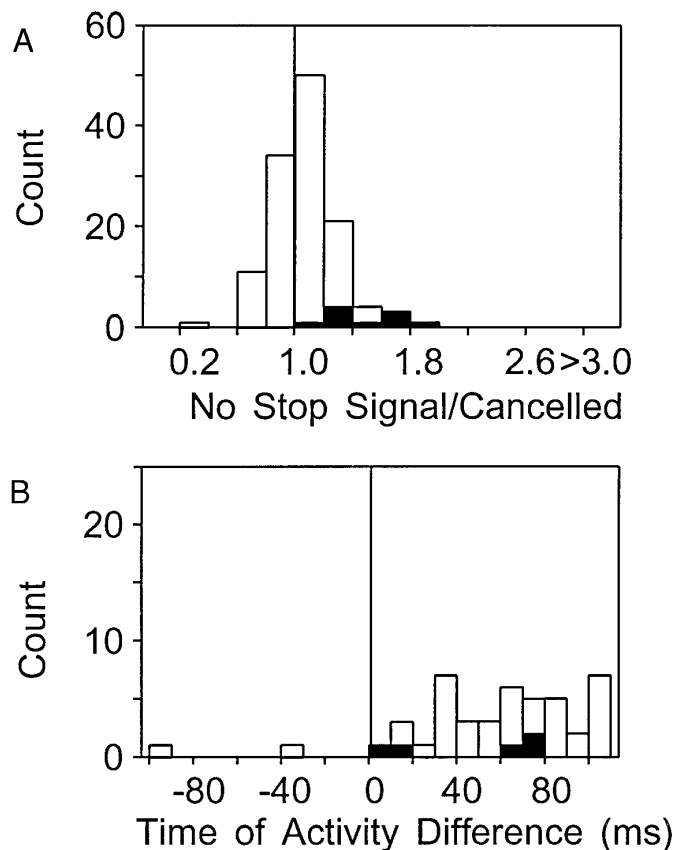


FIG. 11. Comparison of neural activity around the SSRT in cancelled and latency-matched no-stop-signal trials. Conventions as in Fig. 6.

DISCUSSION

Using the countermanding paradigm, we have shown that cells with movement-related and fixation-related activity in the FEF exhibit the necessary characteristics of neurons that are directly involved in regulating the decision of when to shift gaze. Three novel results emerged from the current study. First, a class of neurons was identified in FEF that discharge from fixation until saccade initiation that provide an extraretinal fixation signal and were distinguished from other neurons with foveal receptive fields. Second, both movement and fixation cells discharged differently in trials in which saccade production was inhibited than in trials in which a saccade was initiated. Further, the differential activity occurred within the time period in which the movement was cancelled. This is new evidence showing how movement and fixation cells are involved in saccade programming. Third, the activity associated with movements that were made even though the stop signal was given was not affected by the inhibitory processes invoked by the stop signal. This observation provides new insight into the nature of the interactions between gaze-holding and -shifting mechanisms.

Analytic issues

On the basis of the monkey's behavioral performance during the countermanding task and the race model, we estimated the time at which saccade programming was cancelled. Stop-signal reaction times averaged 97 ms across

three monkeys. This average SSRT is similar to that reported previously in monkeys performing an eye movement countermanding task (Hanes and Schall 1995) but shorter than what has been observed in humans under the same conditions (Hanes and Carpenter 1997). The estimated SSRT was the critical interval in which the neural activity was analyzed to determine whether neurons can play a role in canceling an impending movement. For a given neuron to play a direct role in controlling gaze, the countermanding paradigm requires that the neuron exhibit differential activity associated with cancelled as compared with generated movements and that the difference must occur within the SSRT. Almost all neurons with movement- or fixation-related activity exhibited differential activity in cancelled as compared with no-stop signal at or before the SSRT, but in some cases, the differential activity arose much before or even after the SSRT. Evaluation of this temporal relationship between an inferred cognitive state and an observed neural signal is clearly dependent on the quality of the estimates of the SSRT and of the time of differential activity. We will consider these two measures in turn.

First, there was surely some measurement error in the estimates of the SSRT (Band 1997). All earlier countermanding studies compiled data collected over many sessions. The resulting large number of trials provided well-behaved inhibition functions and orderly no-stop signal reaction time distributions. SSRTs calculated from such large data sets were similar for both methods of estimation described above. This study differed from earlier work in that estimates of SSRT were calculated from the behavioral data that were collected while each cell was recorded. This was important because, like any reaction time, the precise value of SSRT was likely to drift over time according to the monkeys' state. Unless such drifts were accounted for, the interpretation of the neural activity would be compromised. However, the cost of estimating SSRT in this manner was that the data sets were small, so the inhibition function and the distribution of no-stop signal reaction times were not always well behaved. This sometimes resulted in divergent estimates of SSRT based on the two methods employed. There is no theoretical or practical basis on which to decide which method provides the more accurate estimate. Therefore the most conservative approach was to use the average of the SSRTs estimated by the two methods. Besides relating the neural recordings to the SSRT estimated while each cell was recorded, we also related the physiological findings to the overall average SSRT for each monkey. The outcome and resulting conclusions were the same. Therefore, although the data requirements for reliable estimates of SSRT are somewhat stringent, we believe that the estimates of SSRT are not systematically biased and therefore will support reliable comparisons with physiological measures.

Second, we also must consider errors in the estimates of the time of the cancel signal. One form of this error can arise from spike density functions that fluctuate around the threshold of 2 SD above baseline. However, such a fluctuation, which could make the cancellation times appear later, was not common. Typically, the spike density difference function exhibited a monotonic rise from the baseline difference. A related aspect of our analysis of the neural activity that must be considered is that we employed a new filter for

the spike train that might be regarded as introducing a time delay. Many earlier studies of neural activity have created spike density functions by convolving the spike trains with Gaussian filters (e.g., Levick and Zacks 1970; Richmond and Optican 1987). Because no clear criteria have been established to specify the standard deviation of the Gaussian filter, we have devised a filter that resembles the time course of a postsynaptic potential (Hanes and Schall 1996; Thompson et al. 1996). We have compared the performance of the Gaussian filter with that of the postsynaptic potential filter for a subset of the data in the present report. Overall, cancellation times estimated using a Gaussian filter ($\sigma = 4$ and 8 ms) were 5–15 ms earlier than those estimated using the postsynaptic potential filter. Our stance on this issue of what type of filter to use is that the postsynaptic potential filter is a more realistic representation of the neural activity. Spikes recorded in single neurons can only exert influence by generating postsynaptic potentials, thus the time course of synaptic transmission is the most reasonable determinant of neural influence.

Gaze holding signals in the FEFs

An important aspect of the current report is the description of FEF fixation-related neurons in other behavioral tasks besides the countermanding task. Cells with fixation-related activity have been recorded in a number of cortical and subcortical areas including the brain stem (reviewed by Hepp et al. 1989; Keller 1991), superior colliculus (Munoz and Wurtz 1993a), substantia nigra (reviewed by Hikosaka and Wurtz 1989), supplementary eye field (Bon and Lucchetti 1992; Heinen 1995; Schlag et al. 1992), in areas FST and MST (Erickson and Dow 1989; Newsome et al. 1988), and in the inferior parietal lobule (Lynch et al. 1977; Mountcastle et al. 1981; Sakata et al. 1983). Cells with foveal receptive fields and fixation-related activity have been described in previous studies of FEF (Bizzi 1968; Bruce and Goldberg 1985; Segraves 1992; Segraves and Goldberg 1987) and surrounding prefrontal cortex (Suzuki and Azuma 1977; Suzuki et al. 1979).

Like fixation cells in the superior colliculus, the FEF cells with fixation-related activity that we recorded began to discharge after the monkey fixated the central spot and paused before and during the saccade. FEF cells with fixation-related activity discharged for saccades of all directions and most were reactivated after saccade termination. Some of these cells appeared to have weak if any extraretinal modulation although possessing foveal receptive fields. Incomplete testing of some of these neurons prevents reliable estimates of the relative fractions of cells with extraretinal modulation. Nevertheless, with the use of a gap task and a fixation blink task, we now have shown definitively that some FEF fixation-related cells discharge in relation to active fixation and are not just visual cells with foveal receptive fields. The decline in the discharge rate during the gap or blink interval in FEF fixation-related cells is comparable with the decrement in activity observed in superior colliculus fixation neurons in the same conditions (Dorris and Munoz 1996; Dorris et al. 1997; Munoz and Wurtz 1993a). Our description of a physiological gaze-holding signal in FEF complements the recent microstimulation results of Burman and Bruce (1997)

that show inhibition of saccade production after stimulation of some sites in FEF.

Although we have recorded cells with fixation-related activity within the FEF of all three monkeys and have shown that they discharge in a manner appropriate to inhibit saccade production, our sample of fixation cells is limited. In fact, though, the incidence of foveal or fixation responses observed in this study is in accord with previous estimates (Bruce and Goldberg 1985). Despite the sparse number of fixation-related cells within FEF, they represent the second largest population of FEF cells that project to the superior colliculus and to the brain stem saccade generator (Segraves 1992; Segraves and Goldberg 1987). We speculate that the current methods of recordings with metal microelectrodes may undersample fixation cells if they have relatively small cell bodies. Throughout the cortex, projection neurons in layer 5 form a heterogeneous population with diverse but somewhat correlated morphological and physiological characteristics (Fries 1984; reviewed by Gutnick and Mody 1995). Specifically, cells with intrinsic bursting properties tend to have larger cell bodies and dendritic trees than do those with regular spiking properties (Gutnick and Mody 1995). Retrograde tracers injected into the superior colliculus label cells in layer 5 of FEF with large and with small cell bodies (Fries 1984). The fact that FEF cells with strong movement-related activity generate bursts associated with saccades is consistent with the possibility that they are layer 5 pyramidal cells with large cell bodies, whereas the regular spiking pattern of FEF fixation cells suggests that they may have smaller cell bodies. Another possibility is that some fixation cells directly mediate inhibition on movement-related cells in FEF. If this is so, they are likely to be even smaller, GABAergic intrinsic inhibitory neurons, which would make them even harder to isolate with metal microelectrodes.

Another issue to consider is that if FEF is organized in the same topographic manner as the superior colliculus, then fixation cells may be located specifically at the limit of the region where the shortest saccade amplitudes are mapped (Munoz and Wurtz 1993a). In recordings in two of our monkeys, we performed a systematic search in this region and did encounter cells with fixation-related activity somewhat more frequently in penetrations in which movement-related activity was associated with short (2–4°)-amplitude saccades. However, our sample is too small and too few penetrations were made in parts of FEF representing longer (>20°) saccades for firm conclusions to be drawn at this time. Further work is needed to provide more information on this issue.

Cancellation of the gaze-shifting signals in FEF

FEF cells with movement-related activity discharged differently during cancelled as compared with no-stop–signal trials. Moreover, the difference in activity almost always arose within the SSRT. The rise in activity before saccade initiation in no-stop–signal trials suggests that movement-related activity in FEF represents the GO process that is responsible for initiating saccades. In fact, recent work has indicated a precise relationship between the growth of movement-related activity in FEF and saccade initiation (Hanes

and Schall 1996). We showed that saccades are initiated when the activity of individual FEF movement-related cells reaches a specific threshold; the value of this threshold does not vary with saccade latency. The variability of saccade latency seems to arise from stochastic variation in the rate at which the neural activity grows toward that trigger threshold.

Fixation-related cells in FEF exhibited a declining discharge rate before saccade initiation and a rapidly increasing discharge rate when a planned saccade was withheld. This rapid rise in fixation activity coincided with the estimated SSRT. Therefore the rise in fixation activity in cancelled trials may represent the STOP process that is responsible for withholding saccade production.

One remarkable element of these data is the speed of the stopping process. From the data collected for this report as well as earlier data (Schall 1991a), we estimate that the response latencies of cells with foveal receptive fields range from not much <50 ms to only a little more than 90 ms. Given an average SSRT of close to 100 ms and a foveal visual latency of 50 ms, only 50 ms is available for the stopping process to act. In cells firing 100 spikes/s, this amounts to just five spikes. We surmise that under the task conditions used in this study, the reappearance of the fixation spot directly activates a gaze-holding fixation system within the oculomotor system. Our data demonstrate this for FEF, and we suspect the same will hold true for the fixation cells in the superior colliculus (Munoz and Wurtz 1993a).

Independence of gaze-shifting and -holding processes

A central premise of the countermanding race model is that the GO process that initiates a movement and the STOP process that inhibits movement production are stochastically independent, i.e., that the finish times of the two processes are uncorrelated. Previous studies have provided evidence that is consistent with this premise. First, the behavioral predictions based on this model have been supported during the performance of many types of countermanding tasks (reviewed by Logan and Cowan 1984). Also, previously we showed that the peak velocity and saccade amplitude are not different during noncancelled trials in which there are racing GO and STOP processes and latency-matched no-stop–signal trials in which there is only a GO process (Hanes and Schall 1995). Previous ERP studies also have provided evidence that this premise is valid. DeJong and coworkers (1990) showed that the lateralized readiness potential (LRP) over the fronto-central sites was not different during noncancelled and latency-matched no-stop–signal trials. Like the LRP results, the current study has shown that the activity of single FEF neurons is not different in noncancelled and latency-matched no-stop–signal trials. Thus at least at the level of the FEF, the GO process that initiates a movement and the STOP process that inhibits saccade production seem to be independent.

The validity of this independence premise has important implications for models of the oculomotor system. For example, current models of the superior colliculus suggest that saccade production is controlled by a balance of activity between fixation cells and movement-related (buildup) cells in the superior colliculus (Dorris et al. 1997; Wurtz and Optican 1994). This model posits that buildup movement

neurons are inhibited either directly or indirectly by fixation neurons within the superior colliculus. If these models are correct, then the activity of buildup cells, which may represent the GO process, should be less in noncancelled trials than in latency-matched no-stop–signal trials due to the inhibition from fixation cells, which may represent the STOP process. At the level of FEF, however, the activity in noncancelled and latency-matched no-stop–signal trials was not different. Thus, either the independence premise may not be valid at the level of the superior colliculus or models based on interactions between fixation and buildup cells in the superior colliculus may need to be reevaluated. Further work using simultaneous recordings from fixation and buildup neurons in the superior colliculus and elsewhere are necessary to test these alternative explanations.

Effects of countermanding saccades on visual responses

Within the SSRT, the discharge of FEF cells with only visually evoked activity was the same whether a saccade was initiated or inhibited. Because these cells exhibit no movement-related activity, this result seems quite reasonable. To our surprise, however, in 50% of cells with visually evoked activity differential activation arose after the SSRT. When the monkey successfully inhibited saccade production, the activity of these cells decayed even though a visual stimulus was still in the cell's receptive field. On average the differential response occurred 51 ms after the SSRT.

Previous work has shown that the visual response of neurons within FEF is enhanced when a saccade is generated to the peripheral target (Goldberg and Bushnell 1981; Wurtz and Mohler 1976). In the countermanding task, during a majority of trials a saccade was generated to the target that presumably would result in visual enhancement. In cancelled trials, however, after the SSRT, the impending saccade had been cancelled and the visual target was no longer behaviorally relevant. The decrease in the discharge rate of cells with visually evoked activity after the SSRT may reflect this lack of behavioral relevance and thus may represent a form of visual response de-enhancement.

Relation to human countermanding studies

The countermanding paradigm has been used previously in studies using event-related potentials (ERP) to investigate collective neural processes related to inhibiting manual movements (DeJong et al. 1990, 1995). DeJong and co-workers showed a characteristic positive deflection in the lateralized readiness potential unique to cancelled trials that was maximal at fronto-central recording sites in humans. Similar to the results of the current study, the differential activity in cancelled and latency-matched no-stop–signal trials occurred within the SSRT, suggesting that this positivity may reflect a key signal for withholding movement production. Elevated positivity in fronto-central locations has been observed in relation to withheld movements in other go/no-go tasks as well (Kok 1986; Pfefferbaum et al. 1985). Other studies have emphasized differences in N2 and P3 components across go and no-go trials, commonly finding differences in frontal cortex activation when movements are inhibited

(Eimer 1993; Mantysalo 1987; Pfefferbaum and Ford 1988; Pfefferbaum et al. 1985). Thus our results are generally consistent with ERP findings in humans.

Conclusions

In conclusion, previous work has shown the use of physiological manipulations, such as electrical microstimulation and reversible inactivation, for generating links between brain and behavior. In the current report, we have shown that in addition to these commonly used physiological manipulations, behavioral manipulations provide converging evidence about brain and behavior relationships. By implementing the countermanding paradigm, we have shown that cells with movement- and fixation-related activity within the FEF exhibit the necessary characteristics of neurons that are directly involved in regulating the decision of when to shift gaze.

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