

# Contextual Modulation of Substantia Nigra Pars Reticulata Neurons

ARI HANDEL AND PAUL W. GLIMCHER

*Center for Neural Science, New York University, New York, New York 10003*

**Handel, Ari and Paul W. Glimcher.** Contextual modulation of substantia nigra pars reticulata neurons. *J. Neurophysiol.* 83: 3042–3048, 2000. Neurons in the substantia nigra pars reticulata (SNr) are known to encode saccadic eye movements within some, but not all, behavioral contexts. However, the precise contextual factors that effect the modulations of nigral activity are still uncertain. To further examine the effect of behavioral context on the SNr, we recorded the activity of 72 neurons while monkeys made saccades during a delayed saccade task and during periods of free viewing. We quantified and compared the movement fields of each neuron for saccades made under three different conditions: 1) spontaneous saccades, which shifted gaze during periods of free viewing when no stimuli were presented and no reinforcements were delivered; 2) fixational saccades, which brought gaze into alignment with a fixation target at the start of a delayed saccade trial, were necessary for trial completion, but were not directly followed by reinforcement; and 3) terminal saccades, which brought gaze into alignment with a visual target at the end of a delayed saccade trial and were directly followed by reinforcement. For three of the four SNr neuron classes, saccade-related modulations were only present before terminal saccades. For the fourth class, discrete pausers, saccade-related modulations were substantially larger for terminal saccades than for fixational saccades, and modulations were absent for spontaneous saccades. These results and other recent work on the basal ganglia suggest that some saccade-related signals in the SNr may be influenced by the reinforcement associated with a particular saccadic eye movement.

## INTRODUCTION

By examining brain stem afferents to the extraocular motoneurons, movement physiologists have demonstrated the existence of neural signals tightly correlated with the rotational position and velocity of the eye. Upstream from the neurons that carry these signals, neurons of the superior colliculus have been identified that topographically map saccades of all possible amplitudes and directions. A large body of evidence suggests that modulations of collicular activity are also tightly correlated with the generation of eye movements (for a review of these findings see Fuchs et al. 1985; Sparks and Mays 1990).

It seems likely, however, that a nearly perfect correlation between neural activity and movement generation cannot persist in areas that lie even further upstream from the musculature than the colliculus. Goldberg and his colleagues (Bushnell et al. 1981; Goldberg and Bushnell 1981) were the first physiologists to explicitly recognize this possibility in the oculomotor system. In the early 1980s they demonstrated the existence of neurons of the frontal eye fields and posterior parietal cortex that carried saccade-related signals that were modulated by the behavioral context within which a saccade occurred. Hikosaka

and Wurtz (1983a–d, 1985a,b, 1989) extended this concept to studies of the basal ganglia when they demonstrated that the activity of saccade-related neurons in the substantia nigra pars reticulata (SNr), which project to the colliculus, was also correlated with the behavioral context within which a movement occurred.

Although Hikosaka and Wurtz's early studies clearly established that saccade-related signals in the SNr could be modulated by the conditions under which a saccade was produced, an identification of the precise contextual variables that influence nigral modulation has remained a subject of considerable investigation. Recent studies, for example, have demonstrated that many closely related neurons in the basal ganglia may carry information about the value of a movement to an animal: Schultz and colleagues (cf. Hollerman and Schultz 1998; Mirenowicz and Schultz 1996; Schultz 1998; Schultz et al. 1993) have identified signals in the pars compacta subdivision of the substantia nigra (SNc), which receives afferents from the SNr, correlated with the discrepancy between expected and received rewards. Hikosaka and his colleagues (cf. Hikosaka 1991; Hikosaka et al. 1993a,b; Kato et al. 1995; Kawagoe et al. 1998; Kori et al. 1995) have found that neurons in the caudate nucleus, an area that receives afferents from the SNc and projects to the SNr, generate movement-related activity that is correlated with the gain an animal should expect to receive for performing a movement.

To begin to test the hypothesis that, like the caudate and the SNc, the SNr carries contextually modulated signals associated with the reward that an animal can expect to realize for producing a movement, we examined the responses of nigral neurons during saccades made in three contexts: 1) spontaneous saccades, which shifted gaze during periods of free viewing when no stimuli were presented and no reinforcements were delivered; 2) fixational saccades, which brought gaze into alignment with the fixation location at the start of a delayed saccade trial, were necessary for trial completion, but were not directly followed by reinforcement; and 3) terminal saccades, which brought gaze into alignment with a visual target at the end of a delayed saccade trial and were reinforced at short latency. We found that, although all saccade-related SNr neurons were modulated in association with the terminal movements made at the end of a delayed saccade trial, no nigral neurons were modulated for spontaneous movements and only one physiological subclass was weakly modulated for fixational movements.

## METHODS

Seventy-two neurons were recorded from four substantia nigra pars reticulata in three awake-behaving rhesus macaques. During each experiment, eye position was monitored at 500 Hz using the scleral

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search coil technique (Fuchs and Robinson 1966; Judge et al. 1980). Standard behavioral, physiological, and histological procedures were employed as described in detail previously (Handel and Glimcher 1999a). All procedures and protocols were designed in association with the University Veterinarian, approved by the New York University Animal care and use committee, and were in compliance with the U.S. Public health service's *Guide for the care and use of animals*.

We recorded neuronal activity while animals were free to shift gaze around a visually stationary, dimly illuminated room during free periods and while animals made gaze shifts during a delayed saccade task. Free periods were unsignaled, always 2.3 s in duration, and were inserted randomly between 5 and 10% of delayed saccade trials. Delayed saccade trials (Fig. 1) began with an audible beep. Three hundred milliseconds later a central light-emitting diode (LED) subtending  $0.25^\circ$  of visual angle, which appeared yellow to normal human observers, was illuminated and the subject was required to align gaze with this stimulus ( $\pm 3^\circ$ ) within 1,000 ms. Two hundred to 800 ms later, a single yellow eccentric LED was illuminated for 200–1,200 ms, after which the fixation LED was extinguished and the subject was required to shift gaze into alignment with the eccentric LED ( $\pm 3$ – $5^\circ$ ) within 350 ms. If the subject's gaze remained in alignment with the eccentric LED for 350–450 ms, the trial was considered to be performed correctly. Each correctly executed trial was immediately followed by a 300-ms noise burst that served as a secondary reinforcer. In addition, a random 1/5 to 1/3 of correct trials were also followed by delivery of a 0.25-ml drop of fruit juice that served as a primary reinforcer. Eccentric LEDs were placed randomly within 20 horizontal and 20 vertical degrees of the central stimulus. An intertrial interval that ranged from 200 to 3,800 ms followed all free periods and delayed saccade trials.

Terminal saccades were identified as movements produced after fixation stimulus offset that brought gaze into alignment with the eccentric target ( $\pm 3$ – $5^\circ$ ). Fixational saccades were identified from records of each delayed saccade trial and were defined as the first movement ( $\geq 2^\circ$  in amplitude) after trial onset, which brought the point of gaze into alignment with the fixation position ( $\pm 4^\circ$ ). Because fixational saccades were unconstrained in starting point, they were often  $>20^\circ$  in amplitude. The range of fixation saccade amplitudes and directions we sampled thus exceeded the range sampled for terminal saccades that were constrained to fall within the central  $40^\circ$  of the oculomotor range. Finally, during each free period, from 0 to 4 spontaneous saccades ( $\geq 2^\circ$  in amplitude) were identified. Because spontaneous saccades were not constrained either in starting point or ending point, the range of spontaneous saccade amplitudes and directions we sampled also exceeded the range of terminal saccades we sampled.

For each neuron, perievent time histograms were produced using all movements into the quadrant or hemifield (e.g., upper, upper right, lower left, etc.) that produced the largest modulations for the neuron under study (for untuned neurons, movements of all amplitudes and directions were included). Histograms were generated by aligning trials on movement onset and then averaging the data in 25-ms bins and normalizing spike counts/bin to spikes/second. Normalized stan-

dard deviations and standard errors were then computed for each bin to assess both the variance in our samples and the confidence that could be placed in our estimates of mean rate.

The perimovement firing rates associated with all movements were defined as the mean spike rate during the 150-ms period beginning 100 ms before saccade onset. Movement fields were generated for data from all three conditions by plotting perimovement firing rate as function of vertical and horizontal movement amplitude. Plots of movement fields were generated by averaging all observed spike rates within  $2^\circ \times 2^\circ$  bins and plotting average rate as a function of horizontal and vertical movement amplitude. Linear regressions were performed on the unaveraged raw data for each of our three saccade types to identify best-fit planes that described the movement fields.

In a previous description of the terminal saccade data presented here (Handel and Glimcher 1999a), we showed that these planes described nigral response fields at least as well as Gaussian functions for terminal saccade movement fields. Those linear regressions accounted for, on average, 86% of the total variance in each movement field. To determine whether the linear regressions were equally effective at describing spontaneous and fixational movement fields, we also computed variance accounted for by these regressions using the same techniques that we have described for terminal saccades (Handel and Glimcher 1999a).

## RESULTS

In a previous examination of these nigral neurons (Handel and Glimcher 1999a), we described the pattern of firing associated with the terminal movement produced at the end of a delayed saccade task. By analyzing those firing rates we found that saccade-related nigral neurons could be divided into two broad categories: neurons that showed a reduction in firing rate before saccades (pausers) and neurons that showed an increase in firing rate before saccades (bursting). Although saccade-related pausing neurons in the SNr had been described previously (Hikosaka and Wurtz 1983a–d; Joseph and Boussaoud 1985), bursting neurons in the SNr had only been described among skeletomuscular movement-related cells (Schultz 1986). We also found that each of these two categories could be divided into two subclasses. One subclass of pausing cells showed a perimovement decrement in firing rate for terminal movements of all the amplitudes and directions we sampled ( $\pm 20^\circ$  from fixation; universal pausers), whereas others paused more strongly for contraversive movements than for ipsiversive movements (discrete pausers). Nearly all of the bursting neurons that we encountered showed an increase in firing rate for contraversive movements, but one subclass (pause-bursters) showed a decrease in firing rate for ipsiversive movements, whereas the other subclass (bursting) did not.

For this report, we examined the firing rates of these same neurons during spontaneous and fixational movements and compared those data with our previously published description of firing rates during terminal saccades. Figure 2A plots the firing rate of a universal pauser during three metrically similar upward saccades. Note that in the *left* and *middle* panels, which plot spontaneous and fixational movements, respectively, this universal pauser is unmodulated around the time of the upward saccade. In Fig. 2A, *right*, by contrast, the firing rate of the neuron is reduced immediately before the saccade and remains at a reduced level for  $>500$  ms.

To determine how characteristic this response was of all the trials we obtained for this cell, we generated perievent time histograms, centered on movement onset, that averaged firing

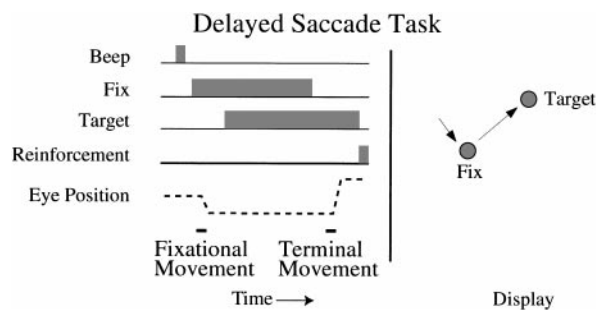


FIG. 1. Temporal sequence of events and display appearance during a delayed saccade trial.

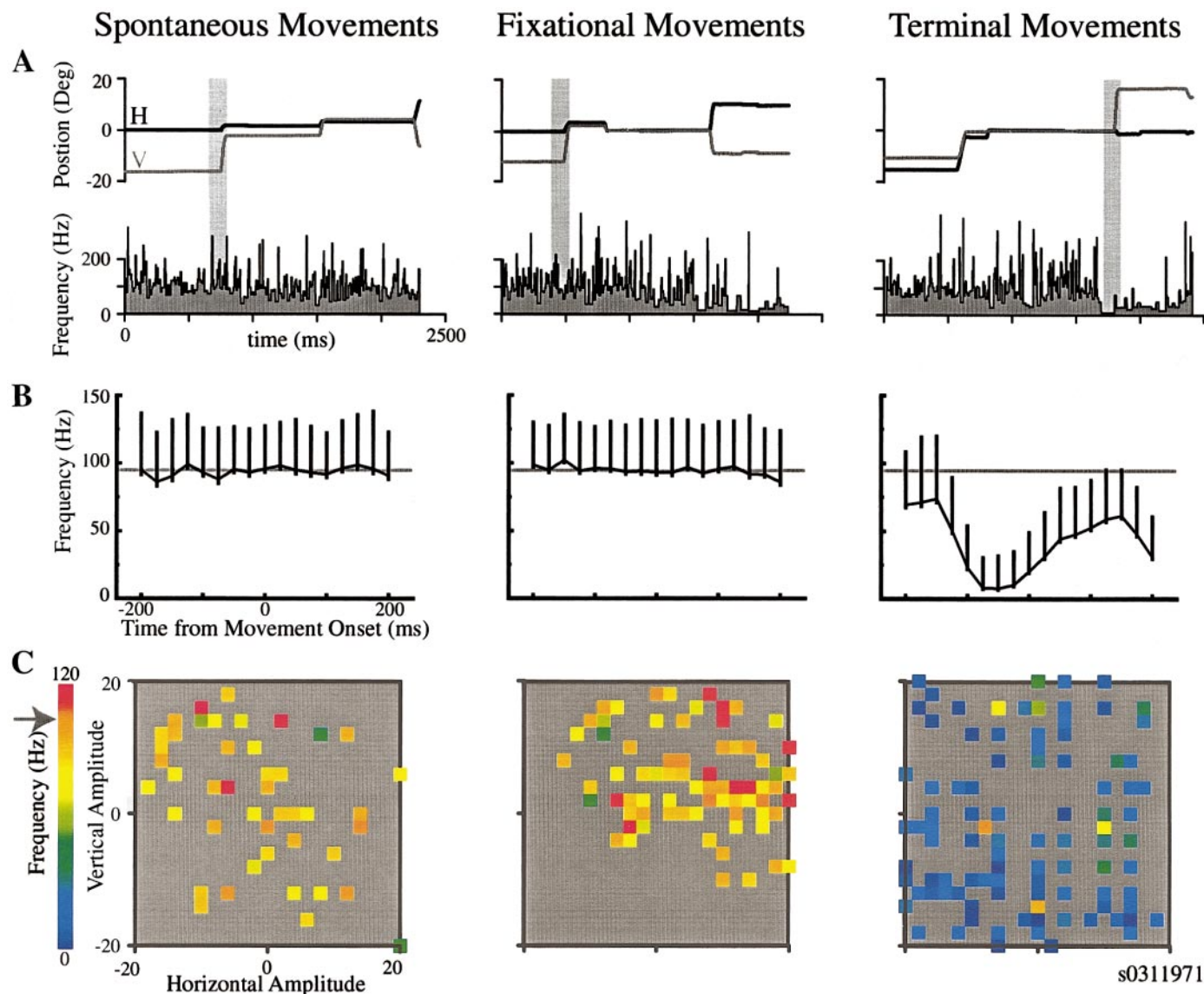


FIG. 2. Comparison of activity of a universal pauser, s0311971, during spontaneous, fixational, and terminal saccades. *A*: single trials showing activity during metrically similar movements. Gray rectangles mark a 150-ms interval beginning 100 ms before movement onset. *B*: peri-event histograms aligned on movement onset for all 3 movement types. Mean rate, standard deviations (upwards bars), and standard errors (downward bars) in 25-ms bins. Because this neuron showed little spatial tuning, we constructed the histograms using all 88, 145, and 151 spontaneous, fixational, and terminal saccades, respectively. *C*: movement fields plotting firing rate during a 150-ms interval beginning 100 ms before movement onset. Data averaged into  $2^\circ \times 2^\circ$  bins and plotted over  $\pm 20^\circ$  of horizontal and vertical amplitude. Gray arrows indicate baseline rate.

rates in 25-ms bins (Fig. 2*B*; upward bars = standard deviations; downward bars = standard errors). Note that although the average firing rate of the neuron began to decrease  $\sim 150$  ms before terminal saccade onset, no modulation was apparent at any time in association with either spontaneous or fixational movements.

To quantify this relationship and to account for the fact that most nigral neurons are spatially tuned with regard to movement amplitude and direction, we plotted the firing rate of each neuron immediately before and during spontaneous, fixational, and terminal saccades, as a function of horizontal and vertical movement amplitude. Figure 2*C* presents these movement fields that plot raw data for spontaneous movements, fixational movements, and terminal movements averaged into  $2^\circ$  bins with mean firing rate coded in color. Note that during all

terminal movements the firing rate of the neuron dropped to nearly zero. In contrast, during all spontaneous and fixational movements the firing rate of the neuron remained at baseline levels, which are indicated by the gray arrow.

Like the neuron shown in Fig. 2, most nigral neurons were not modulated during either spontaneous or fixational movements. However, as shown in Fig. 3 for a discrete pauser, we did find that some neurons were weakly modulated during fixational saccades. Figure 3*A* plots neuronal activity during three metrically similar up-right movements. Note that the neuron appears weakly, if at all, modulated before a spontaneous saccade, clearly modulated before a fixational saccade, and profoundly modulated before a terminal saccade. The peri-event time histograms indicate that for this neuron there was, in fact, a repeatable modulation associated with fixational movements

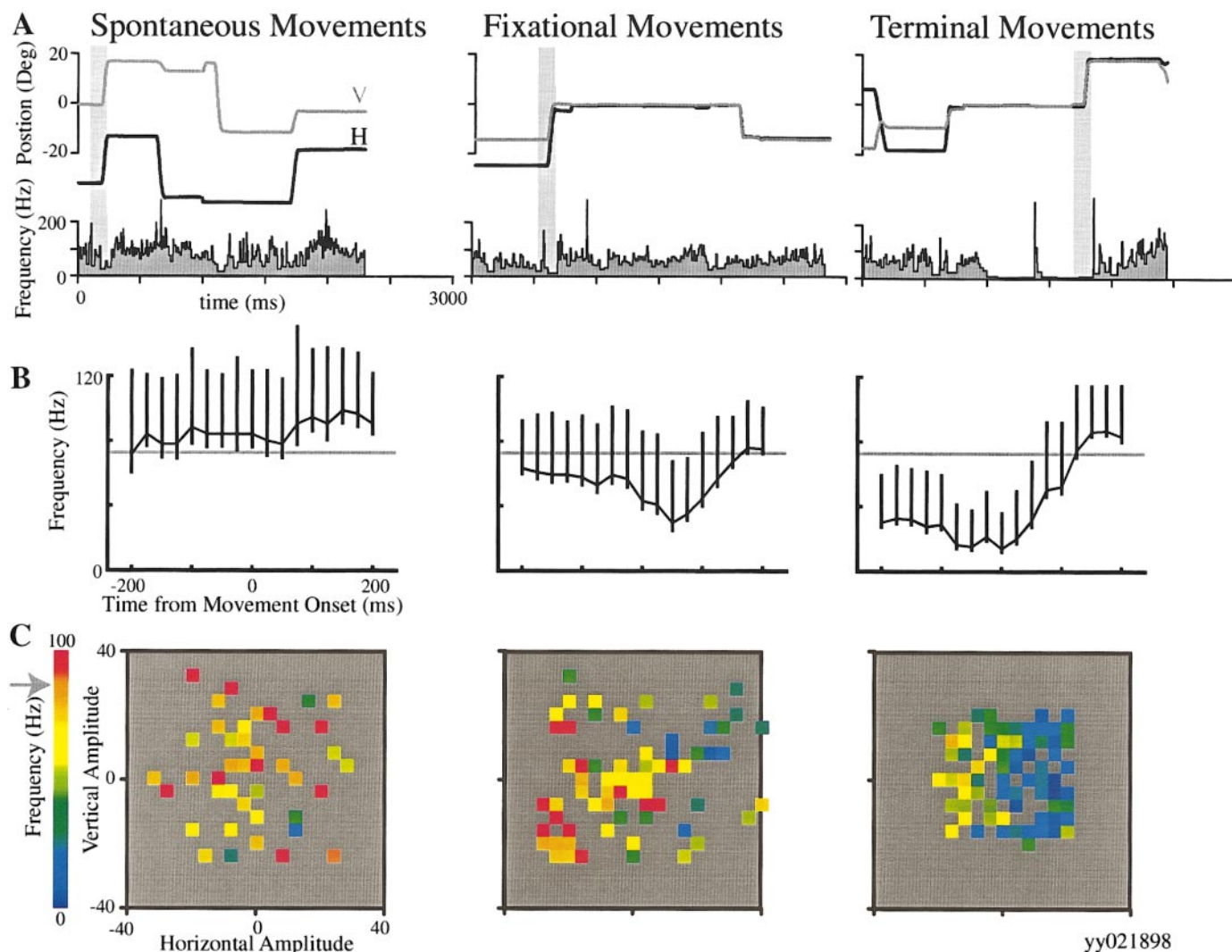


FIG. 3. Comparison of activity of a discrete pauser, yy021898, during spontaneous, fixational, and terminal saccades, as in Fig. 2. *A*: single trials. *B*: perievent histograms for all 19, 50, and 65 spontaneous, fixational, and terminal saccades, respectively, with horizontal amplitudes greater than  $+2^\circ$ . *C*: movement fields. Data are averaged in  $4^\circ \times 4^\circ$  bins and plotted over  $\pm 40^\circ$  (note scale change to include additional data) of horizontal and vertical amplitude.

that was about one-half the size of the modulation associated with terminal movements.

The movement fields plotted for this neuron in Fig. 3C reveal that these modulations were spatially tuned: the neuron paused more strongly for rightward (contraversive) fixational movements than for leftward movements, just as it paused more strongly for rightward than for leftward terminal saccades.

To provide a statistical test of the hypothesis that some or all of the population of nigral neurons are unmodulated during spontaneous and fixational saccades, we fit each of the three movement fields, for all neurons, with planar regressions and then analyzed the parameters that described those regression planes for our nigral population. Figure 4 plots the total variance accounted for by the planar regressions for all three types of movement fields. The planar regressions accounted for, on average, 91% the variance associated with spontaneous movements and 90% of the variance associated with fixational movements. Thus the regressions did at least as good a job describing spontaneous and fixational movement fields as they

did describing terminal movement fields (Handel and Glimcher 1999a).

We therefore used the average modulation and spatial tuning estimates derived from the planar fits to the three movement fields measured for each neuron to compare the degree to which SNr neurons encoded spontaneous, fixational, and terminal saccades. The results of this comparison for universal pausers, bursters, and pause-bursters are shown in Fig. 5. The *left panel* of Fig. 5A plots the average modulation for spontaneous saccades as a function of the average modulation for terminal saccades, for each neuron. Note that, for terminal saccades, the average modulations in firing rate across this population, which included both bursters and pausers, spanned a range of  $>200\%$ . In contrast, for spontaneous saccades, the average modulation for all of these neurons was very close to 0%. Similarly, the *right panel* of Fig. 5A shows that the tuning strength for spontaneous saccades rarely exceeded 1 spike/s/deg, whereas the tuning strength for terminal saccades ranged up to 3 spike/s/deg. A similar pattern is apparent in the comparison between fixational saccades and terminal saccades

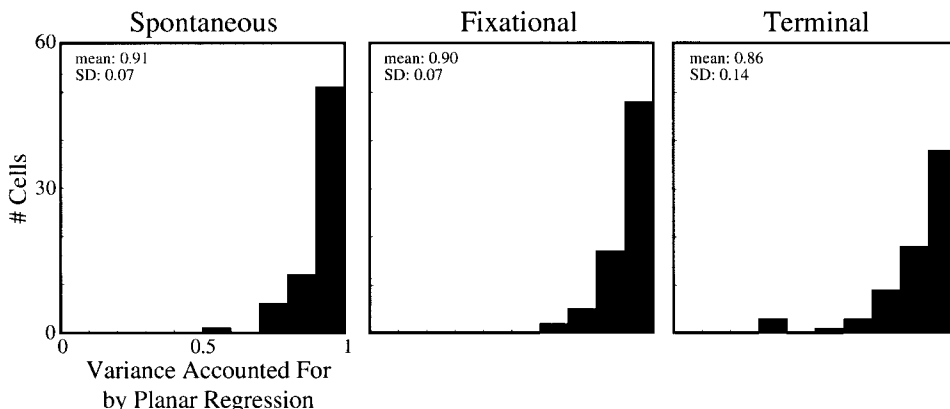


FIG. 4. Histograms of the variance accounted for by planar regressions fit to movement fields gathered for spontaneous, fixational, and terminal saccades. Terminal saccade data have been previously reported. For more details and methods see Handel and Glimcher (1999a).

(Fig. 5B). Although there were a few neurons that were very weakly tuned for terminal saccades but showed some tuning for fixational saccades (Fig. 5B, right panel), across this population the average modulation and tuning strength were small for fixational saccades even when they were large for terminal saccades.

We tested, for each of these three types of neurons, the hypothesis that the modulations for spontaneous or fixational saccades were statistically indistinguishable from the modulations of these neurons for terminal saccades. For all three groups of neurons were able to reject the null hypothesis (by *t*-test) for either the slope of the movement fields, their mean rates, or both, leading us to conclude that the modulations of

these neurons during spontaneous and fixational saccades are different than during terminal saccades (see Fig. 5 legend). In fact, for all three classes the linear correlations between the movement field parameters for spontaneous and terminal movements were insignificant. Other than a weak effect for the spatial tuning in pause-bursters, there were also no significant correlations between fixational and terminal saccades movement field parameters for these classes.

A different pattern was seen for discrete pausers (Fig. 6). Like the other cell classes, there was very little average modulation in firing rate for either spontaneous (Fig. 6A, left panel) or fixational saccades (Fig. 6B, left panel) even in neurons with large average modulations in activity for terminal saccades. However, unlike other SNr cell classes, many discrete pausers did show spatially tuned decreases in activity before fixational saccades. On average, however, the responses of discrete pausers for fixational saccades tended to be only half as large as the responses of these neurons for terminal saccades (Fig. 6B, right panel: slope = 0.46; correlation,  $P < 0.0005$ ). A statistical analysis of these modulations, however, did permit us to reject

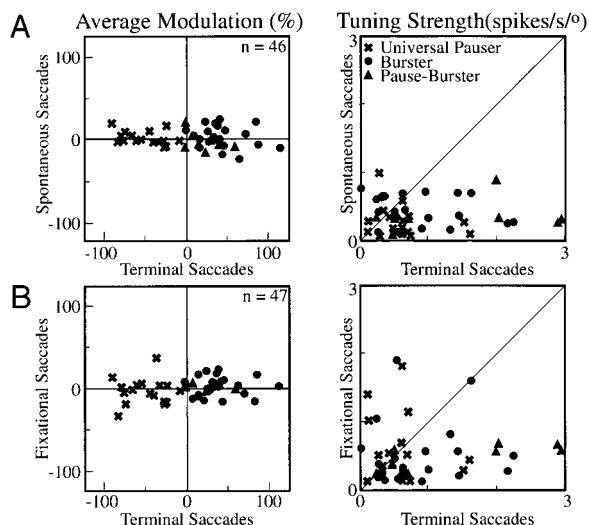


FIG. 5. Comparison of movement field regression parameters for all universal pausers (x), bursters (●), and pause-bursters (▲). *A*: correlations between spontaneous saccade and terminal saccade average modulation across all possible movements (intercepts from movement field regressions; left) and tuning strength (slope amplitudes from movement field regressions; right). Average modulation (%; by linear correlation):  $y = -0.029x + 2$ , significance:  $P = 0.411$ . Significance of the difference between spontaneous and terminal saccades by *t*-test: universal pausers,  $P < 0.001$ ; bursters,  $P < 0.001$ ; pause-bursters,  $P = 0.055$ . For tuning strength (spikes/s/deg):  $y = -0.015x + 0.390$ , and significance:  $P = 0.763$ . *t*-Test significance: universal pausers,  $P < 0.05$ ; bursters,  $P < 0.05$ ; pause-bursters,  $P < 0.05$ . *B*: correlations between the average modulation (left) and the tuning strength (right) for fixational and terminal saccades. For average modulation (%):  $y = 0.053x - 7$ , and significance:  $P = 0.179$ . *t*-Test significance: universal pausers,  $P < 0.001$ ; bursters,  $P < 0.001$ ; pause-bursters,  $P = 0.055$ . For tuning strength (spikes/s/deg):  $y = 0.026x + 0.515$ , and significance:  $P = 0.771$ . *t*-Test significance: universal pausers,  $P = 0.841$ ; bursters,  $P = 0.057$ ; pause-bursters,  $P < 0.05$ .

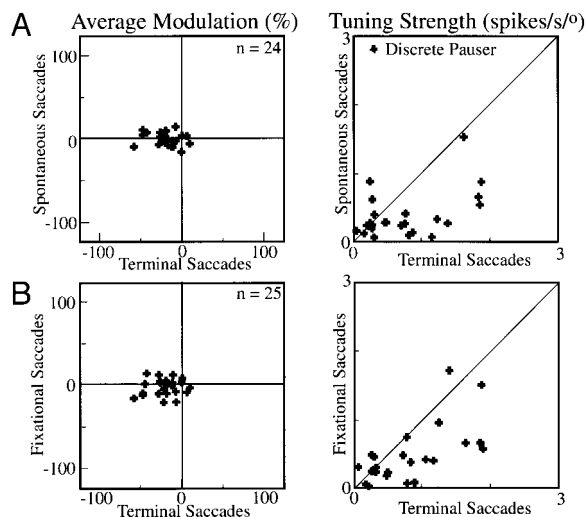


FIG. 6. Comparison of movement field regression parameters for all discrete pausers (+) as in Fig. 5. *A*: correlations between spontaneous and terminal saccades. For average modulation (%):  $y = -0.115x + 7$ , and significance:  $P = 0.225$ . *t*-Test significance:  $P < 0.001$ . For tuning strength (spikes/s/deg):  $y = 0.269x + 0.178$ , and significance:  $P = 0.018$ . *t*-Test significance:  $P < 0.005$ . *B*: correlations between fixational and terminal saccades. For average modulation (%):  $y = 0.064x - 11$ , and significance:  $P = 0.585$ . *t*-Test significance:  $P < 0.001$ . For slope amplitudes (spikes/s/deg):  $y = 0.464x + 0.110$ , and significance:  $P = 0.0004$ . *t*-Test significance:  $P < 0.005$ .

the null hypothesis (by *t*-test) that these neurons behaved in the same manner during fixational and terminal saccades (see Fig. 6 legend). Some discrete pausers also showed spatially tuned decreases in activity before spontaneous saccades, although these responses tended to be even weaker (Fig. 6A, *right panel*: slope = 0.27; correlation,  $P < 0.05$ ). Thus discrete pausers appear to encode all three types of saccades, but in a manner that appears to be correlated with the reinforcement that can be expected to result from each type of movement.

## DISCUSSION

In summary, we replicated the original finding by Hikosaka and Wurtz (1983a) that saccade-related neurons of the SNr are modulated during terminal saccades produced in a delayed saccade task but largely unmodulated during spontaneous saccades produced while the animal is seated in a dimly illuminated stationary environment. We also examined fixational saccades, which, like terminal saccades, shifted gaze into alignment with an experimenter defined location within the context of an operant task. Unlike terminal saccades, however, these fixational saccades were not followed by a reinforcement at short latency. We found that nigral universal pausers, pause-bursters, and bursters were unmodulated during these fixational movements. Nigral discrete pausers were relatively weakly, but significantly, modulated during these fixational movements. These data may suggest that at least some neurons in the SNr carry a signal related to the reinforcement associated with an eye movement.

This conclusion should be tempered by the observation that, of the saccades we studied, only the terminal saccades always shifted gaze from a central starting position to an eccentric ending position. Both the spontaneous and fixational saccades began with the eye at a variable starting position within the orbit. This observation, however, is unlikely to account for our findings for two reasons. First, the initial eye position for many spontaneous saccades were similar to the initial eye position for terminal saccades, and yet we found no evidence that any of the spontaneous saccades we examined were associated with rate modulations in universal pausers, pause-bursters, or bursters. Second, when SNr activity has been previously examined while subjects made saccades from different starting positions, no effect of orbital position on neuronal activity has been reported (Bayer and Glimcher 1999; Hikosaka and Wurtz 1983a).

When Hikosaka and Wurtz (1983a–d, 1985a,b) first examined the saccade-related SNr nearly 20 yr ago, they concluded that unlike many brain stem and cortical areas, the SNr encoded saccade-related signals in a contextually dependent manner. Many nigral neurons were inhibited before saccades under some environmental contexts but not under others. In their preliminary examination of these saccadic contexts, they noted that some neurons were more strongly inhibited during tasks which 1) imposed a memory requirement on the subject, 2) required that saccades be produced at a very precise time, and 3) imposed very specific constraints for reinforcement. In light of existing data suggesting that the basal ganglia were preferentially involved in the generation of movements guided by remembered stimuli (cf. Divac et al. 1967; Leigh et al. 1983; Rosvold et al. 1958), they interpreted their data to suggest that the SNr might be specialized to disinhibit brain stem saccadic

circuitry before memory saccades (cf. Hikosaka and Wurtz 1989). Further, because the flow of signals through the oculomotor SNr was then believed to originate largely in the saccade-associated frontal eye fields and to reach the SNr via the caudate, they proposed a general frontal eye fields-caudate-SNr circuit for the gated activation of the topographically mapped superior colliculus during memory saccades.

Many of the assumptions on which that original theory was based have been refined over the past 20 yr. First, the work of Schultz (cf. Hollerman and Schultz 1998; Mirenowicz and Schultz 1996; Schultz 1998; Schultz et al. 1993) and Hikosaka (Hikosaka 1991; Hikosaka et al. 1993a,b; Kato et al. 1995; Kawagoe et al. 1998; Kori et al. 1995) has suggested that the responses of neurons in the basal ganglia may be more tightly tied to the reinforcement or gain that an animal can expect to receive than to simple properties of the sensory stimulus guiding the movement. Second, new anatomic evidence (Middleton and Strick 1996) suggests that afferents and efferents of the SNr outside the basal ganglia include not only the frontal eye fields and the superior colliculus but also a number of other cortical areas believed to play a role in visual perception and saccade planning. Third, our own work (Handel and Glimcher 1999a,b) has shown that not only does the SNr also contain saccade-related bursting neurons undescribed by Hikosaka and Wurtz but that when saccade-related nigral neurons are examined with identically reinforced memory and nonmemory tasks, the nigral population is not preferentially modulated before memory saccades.

At least some of these observations have been interpreted to suggest that a principal function of the basal ganglia is to predict the magnitude and timing of future reinforcements and to identify errors in those predictions (cf. Schultz et al. 1997). Both theoretical and experimental work conducted over the past several years has identified signals of these types as critical for response selection and generation (cf. Hikosaka 1991; Hollerman and Schultz 1998; Kawagoe et al. 1998; Platt and Glimcher 1999). If, as these observations suggest, the basal ganglia serves as a source for signals of this type and these signals are critical for behavioral control, then output nuclei like the SNr might be expected to carry signals of this type beyond the basal ganglia. Our data begin to suggest that the SNr, a principal motor-related output nucleus of the basal ganglia, carries a signal related to the reinforcement an animal can expect to receive for producing an eye movement in an operant task.

To more fully test this hypothesis, it will be necessary to design experiments in which animal subjects specifically communicate an estimate of the gain that they expect to receive for a behavioral response. These behaviorally measured estimates, or psychometric functions, could then be correlated with physiologically derived neurometric functions for neurons in the SNr.

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Address for reprint requests: P. W. Glimcher, Center for Neural Science, 4 Washington Place, 809, New York, NY 10003.

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