Correction to:

Eye position and memory saccade related responses in substantia nigra pars reticulata

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Figure 7 on page 435 should appear on page 436 with the caption on page 436.

Figure 9 on page 436 should appear on page 435 with the caption on page 435.

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RESEARCH ARTICLE

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Eye position and memory saccade related responses in substantia nigra pars reticulata

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Abstract The substantia nigra pars reticulata (SNr), a major output nucleus of the basal ganglia, has been implicated anatomically, pharmacologically and physiologically in the generation of saccadic eye movements. However, the unique contribution of the SNr to saccade generation remains elusive. We studied the activity of SNr neurons while rhesus monkeys made saccades from different initial orbital positions, to determine what effects, if any, eye position had on SNr neuronal activity. We found that there was no effect of eye position on SNr neuronal responses. We also examined the responses of SNr neurons during memory-guided saccades to determine whether SNr discharges were affected by whether the target of the upcoming saccade was visible. We found that there was no change in response properties during memory saccade trials as compared to otherwise identical visually guided trials. SNr neurons appear to carry no information about either eye position or whether a movement is guided by a visible or remembered target. These results suggest that nigral signals are encoded in the same coordinate frame as those in the SC and FEF, but that unlike neuronal responses in these areas, SNr activity is not influenced by whether the saccade target remains visible until the movement is executed.

Keywords Substantia nigra pars reticulata · Saccade · Oculomotor · Memory · Orbital position

Introduction

The physiological investigations of Hikosaka and Wurtz (1983a, 1983b, 1983c, 1983d) unequivocally demonstrated a relationship between the SNr and saccades. They identified a population of nigral neurons with high tonic firing rates that paused around the time at which an eye movement was produced in an operant task. In their tasks, each nigral saccade-related neuron was selectively modulated before a subset of movements having a limited range of amplitudes and directions. Many of these neurons also showed modulations at the onset of a visual stimulus which was the target of a future saccade. These modulations persisted during intervals when the visual stimulus was extinguished if the animals would later shift their gaze to the remembered location. Subsequent experiments even demonstrated that reversible inactivation of this area disrupted saccade production (1985b). Taken together, these findings strongly suggest that neurons in the SNr are involved in the generation of saccades.

Further studies of nigral neurons during saccades were performed by Handel and Glimcher in 1999. They reported that in addition to the pausing neurons discovered by Hikosaka and Wurtz, there is a second population of neurons in the SNr which show an increase in firing rate in association with saccades, which they called bursters, a result recently confirmed by Sato and Hikosaka (2002). The response properties of the neurons appear to be generally similar to those of neurons which show decreases in activity (pausers). Both classes of neurons show similar patterns of modulation in association with saccades; the only difference is whether that modulation is an increase or decrease in firing rate from baseline.

SNr neurons have also been implicated anatomically in the generation of saccades, as they are known to project (both directly and indirectly) to several integral oculomotor structures. The work of Rinvik and colleagues (1976), as well as that of Jayaraman (1977), showed that there is a dense inhibitory projection from the SNr to the middle layers of the superior colliculus (SC), a neural structure known to be crucial for the generation of saccades. More recent work by Lynch et al. (1994) has identified a subset of neurons in the lateral part of the SNr that connects, through the thalamus, with neurons in the frontal eye fields (FEF), a cortical eye movement control area. In fact, a significant proportion of SNr neurons send axon collat-

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erals to both the thalamus and the SC (Parent et al. 1983). These anatomical results provide further evidence that the SNr carries information that contributes to the control of saccadic eye movements.

Although SNr neurons have been implicated both physiologically and anatomically as part of an oculomotor control circuit containing the SC and the FEF, nigral neurons are known to show response patterns different from those of neurons in the SC and FEF. By recording SNr neuronal responses during movements of a wide range of amplitudes and directions, Handel and Glimcher were able to determine that the spatial structure of the responses of both pausing and bursting neurons can be described as roughly planar; firing rate is as well described as a linear function of movement amplitude as it is by a gaussian function, even though the linear functions required fewer free parameters to accomplish this description. This is surprising since the SNr projects to both the superior colliculus (SC) and the frontal eye fields (FEF), where the spatial structure of neuronal responses is better described by a gaussian function than a linear function.

SNr neurons also differ from those in the SC in their responses to movements outside of operantly conditioned tasks, movements known as spontaneous saccades. Neurons in the SC are modulated during spontaneous saccades (Goldberg and Wurtz 1993), while neurons in the FEF are not (Bruce and Goldberg 1985). Handel and Glimcher (2000), continuing an earlier line of investigation by Hikosaka and Wurtz (1983a), demonstrated that SNr neurons are completely unmodulated during spontaneous saccades. These results suggest that the SNr sends signals to both the SC and FEF that may make a unique contribution to the saccadic control system

We hypothesized that if we could produce a clearer view of how signals in the SNr might be combined with signals in other areas involved in the generation of saccades, we might better understand the role of the SNr in the production of saccades. To produce such a comparison, we undertook a quantitative study of the modulation of SNr neuronal discharges during two tasks which have been well studied in other areas of the brain involved in saccade generation. By studying the response properties of SNr neurons during saccades initiated from different orbital positions, we were able to determine whether they were similar enough to the responses of their target structures (the SC and FEF) to provide saccade-related input in the same coordinate reference frame as one or more of the target structures. In addition, by studying SNr responses during saccades to remembered target locations and comparing these responses to activity on otherwise identical visible target trials, we could determine whether this activity would be suitable to drive related responses observed in the SC and the FEF. Response properties during these two types of tasks have been well studied in both of these oculomotor structures, creating a framework into which we could integrate the responses we observed in SNr neurons.

Eye position related responses

The effect of eye position on neuronal responses has been investigated in many of the brain areas which contribute to saccade generation. In the FEF, peri-saccadic firing rate is correlated with the amplitude and direction of a saccadic eye movement, largely independent of the initial or final position of the eye in the orbit (Goldberg and Bruce 1990). In the colliculus, the presence of eye position signals has been more controversial. Some physiological data seem to suggest that the SC, like the FEF, encodes only saccadic amplitude and direction (Mays and Sparks 1980), although there is also evidence that an orbital position signal may influence collicular activity (Van Opstal et al. 1995). In addition, many neurons in the lateral intraparietal area of the posterior parietal cortex (LIP), an area with known projections to the SC and the FEF (Lynch et al. 1985, Barbus and Mesulam 1981), carry signals that encode the amplitude and direction of a saccade as well as the position of the eye. The work of Andersen and colleagues (1990) showed that although these neurons always respond most strongly for a subset of movements with a limited range of amplitudes and directions, the magnitude of the neuronal response for all movements is modulated by the position of the eye. In their original studies, Hikosaka and Wurtz reported anecdotally that orbital position had little effect on SNr neuronal responses, but whether eye position has a significant effect on the response properties of SNr neurons has not been systematically examined. Detailed information about the orbital position responses of SNr neurons could suggest how they might be related to the eye movement command signals in these other saccade related areas.

Memory saccade related responses

Studying the activity of nigral neurons during saccades to remembered targets also presents the opportunity to compare activity across multiple brain areas that contribute to saccade generation. The SC, FEF, and LIP have all been shown to exhibit activity immediately before saccades to remembered target locations. In all of these areas the neuronal activity before saccades to remembered targets is similar to or weaker than activity during visual target presentations. In their original survey of the SNr, Hikosaka and Wurtz (1983c) reported that many SNr neurons were responsive during saccades to remembered targets, but they did not quantitatively compare this modulation to that produced immediately before visually guided saccades in their primary dataset. Quantitatively comparing SNr activity during both visually and memory guided saccades might reveal more about the unique role of SNr neuronal responses in the generation of saccades.

Summary of results

In this study we examined the responses of nigral neurons during movements from different initial eye positions, as well as responses during movements to remembered target locations. We found that there was no effect of eye position on the activity of SNr neurons, and that the activity of SNr neurons associated with saccades to remembered targets was no different from the activity associated with visually guided saccades in otherwise identical trials. The results of our experiments suggest that nigral neurons do not carry information about eye position or about whether a movement is guided by a visible or remembered target. Coupled with the observation that these neurons preferentially encode movements that are followed by a reinforcement (Sato and Hikosaka 2002), as well as the other reward related signals which have been reported in the basal ganglia, signals from the SNr appear ideal for integrating the context of movements (e.g. reinforcement information), rather than directly controlling movement execution, a hypothesis originally suggested by Hikosaka and Wurtz in 1985 and more recently proposed by Handel and Glimcher (2000).

Materials and methods

Four male rhesus macaques (*Macaca mulatta*) were used as subjects. All animal procedures were developed in association with the University Veterinarian, approved by the New York University Institutional Care and Use Committee, and designed and conducted in compliance with the Public Health Service's Guide for the care and use of animals. All surgical and training procedures were performed using standard protocols that have been described in detail previously (Handel and Glimcher 1997).

Tasks

Monkeys were trained to perform two tasks, a memory saccade task and a delayed saccade task. Memory saccade trials (Fig. 1A) began with an audible beep. Three-hundred milliseconds later a central light emitting diode (LED), which appeared yellow to normal human observers, was illuminated and the subject was required to align gaze with this stimulus (±3°) within 1,000 ms. Two hundred to 800 ms after gaze was aligned with this central LED, a single yellow eccentric LED was illuminated for 400–1,000 ms and extinguished. After a further 200–1,000 ms memory interval, the central LED was extinguished (the Go cue), and the subject was required to shift gaze into alignment with the remembered location of the eccentric LED (±3–6°) within 350 ms. If the subject's gaze remained in alignment with the remembered location of the eccentric LED for 300 ms, the trial was considered to be performed correctly.

Delayed saccade trials (Fig. 1B) were similar, but 400–1,000 ms after the eccentric LED was illuminated, the central LED was extinguished (the Go cue) and the subject was required to shift gaze into alignment with the eccentric LED (±3–5°) 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.

Usually, trials of each task were run in separate blocks, but on a few occasions they were randomly interleaved. In all cases, trials were run in dim illumination with an inter-trial interval of 200–800 ms. Eccentric LED locations for both tasks were chosen pseudo-randomly with replacement. Correct trials were reinforced with a

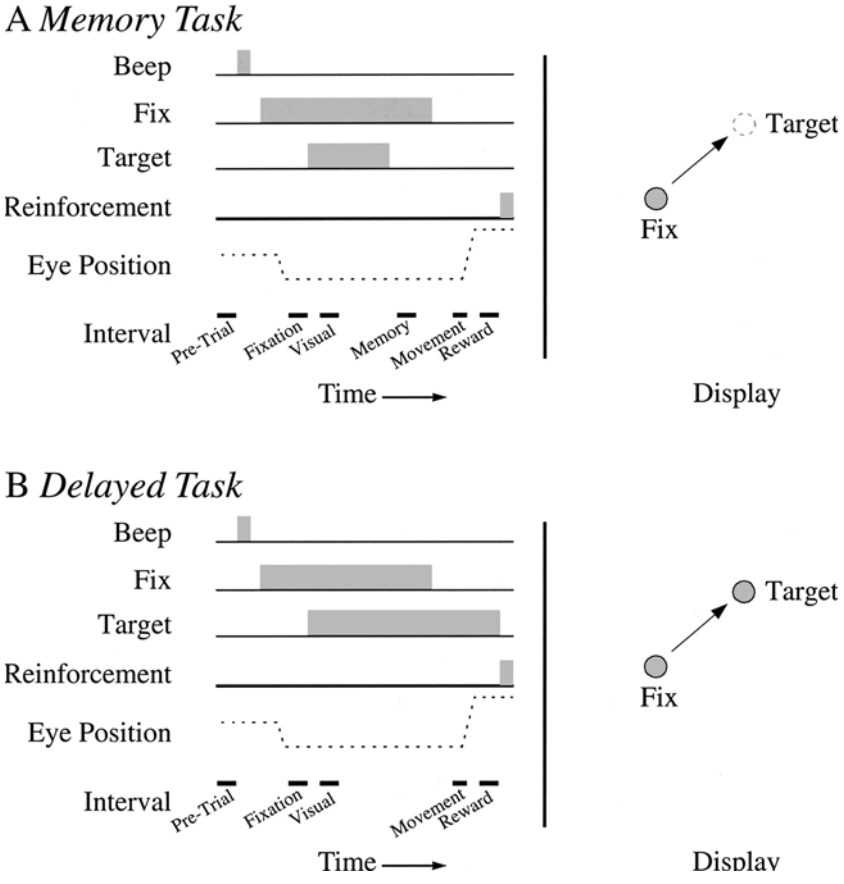

Fig. 1 **A** *Left* Temporal sequence of events, and measured intervals; *right* display appearance during a memory saccade trial. **B** A delayed saccade trial as a function of time and as the display appeared to the subject

300 ms noise burst that was randomly supplemented with fruit juice on one-third to one-fifth of trials.

On days when we studied the effect of orbital position, subjects first performed a block of delayed saccade trials in order to identify a subset of movements for which the cell was maximally modulated. Subjects then ran a block of delayed saccade trials in which the vertical component of the saccade was fixed at the elevation of the movement evoking the best response, while the horizontal component was varied across 40! of visual angle. During this phase of the experiment, the fixation LED appeared with equal likelihood at one of three locations: straight ahead, 12° to the left, or 12° to the right. The secondary target always appeared at a location which was the same vertical distance from the fixation LED, but on each trial, it could appear at any one of ten different horizontal locations. This allowed us to collect data which could be separated into three response sets (or tuning curves), one from each origin.

Neurons for which we recorded memory saccade related activity were localized histologically. However, during the orbital position experiments, we used ultrasonography (Glimcher et al. 2001) to place guide tubes in the approximate location of the lateral part of the SNr. Neurons at the anatomical location of the SNr as determined by ultrasonography were classified as nigral based on their similarity in both location and physiological properties to the neurons in the memory saccade experiment and those studied in previous work by the laboratory (Handel and Glimcher 1999, 2000).

Single neuron analyses

Single trial measurements

For each correctly performed delayed saccade trial, we measured the horizontal and vertical amplitude of the saccade that aligned gaze with the eccentric LED as well as the firing rate of the neuron during five intervals: a 200 ms Pre-Trial interval ending at the onset of the beep that initiated the trial; a 200 ms Fixation interval ending at the onset of the eccentric LED; a 200 ms Visual interval beginning 50 ms after the onset of the eccentric LED; a 150 ms Movement interval beginning 100 ms before the onset of the saccade; and a 200 ms Reward interval ending at the delivery of reinforcement. For memory saccade trials we measured the firing rate of the neuron during each of these intervals as well as during a 200 ms Memory interval beginning 50 ms after the offset of the eccentric LED. For delayed saccade trials collected during the orbital position experiment, we used a 200 ms movement interval beginning 100 ms before the onset of the saccade.

Response fields

In a second step of data analysis we generated six memory saccade and five delayed saccade response fields for each neuron, one response field for each measured interval. Each response field plotted the firing rate of the neuron during the measured interval on each correctly completed trial as a function of the horizontal and vertical amplitude of the saccade made at the end of the trial. To quantify the relationship between the firing rate during an interval and the horizontal and vertical amplitude of the saccade made at the end of the trial, we fit each response field with a planar regression. (For comparison, we also fit each response field with a two-dimensional Gaussian model which never fit the data more efficiently than a linear regression. See Table 1. For a detailed discussion of this issue and the constraints placed on these gaussian models see Handel and Glimcher 1999.)

To check that our linear regressions did not systematically distort our response fields, we calculated, for each neuron, the firing rate predicted by the regression and subtracted it from the observed firing rate of the neuron. We then averaged these residuals into 4°×4° bins and plotted them as a function of horizontal and vertical movement amplitude, where a systematic overestimation or underestimation of firing rate for some range of horizontal and vertical movement amplitudes would be apparent.

Table 1 Variance accounted for by planar regressions/Gaussian fits, computed as (total variance−residual variance)/total variance, where variance was defined as the sum of the squared cartesian distances between the data and zero

	Delayed saccade	Memory saccade
Fixation	89%/90%	90%/90%
Visual	89%/90%	89%/90%
Memory	n/a	90%/91%
Movement	90%/91%	90%/91%
Reward	94%/95%	94%/95%

We examined the overall efficiency of the linear regressions, the extent to which they accounted for the firing rates of the neurons, during both memory saccade and delayed saccade trials. This allowed us to determine whether the response fields of nigral neurons increased in variability when a memory interval was imposed. We performed this analysis by computing the variance accounted for by the linear regressions during the four intervals that were common to both tasks: the fixation interval, the visual interval, the movement interval and the reward interval. [Variance accounted for was computed as (Total variance−Residual variance)/Total variance, where variance was defined as the sum of the squared cartesian distances between the data and zero; for details see Handel and Glimcher 1999]. By comparing the variance accounted for by the linear fits under both conditions, we were able to ask whether there was a systematic increase or decrease in the variance of neuronal firing rate when a memory interval was imposed.[1]

In order to provide a sense for how neuronal responses were influenced by saccade amplitude and initial orbital position, we created tuning curves by segregating all the movements into three groups based on initial orbital position. For each group, we then averaged the firing rates for movements with similar amplitudes, and plotted the three groups on a single set of axes. For comparison, we also averaged firing rates for movements with similar endpoints and plotted these three curves on a single set of axes. In this format, for example, it would be apparent if responses for movements from one of the eccentric origins were significantly larger (or smaller) than movements from the central origin.

In order to quantify this relationship for both amplitude and endpoint, we fit all of the data used to construct the two plots described above using an adaptive minimization algorithm with an arctangent function containing four free parameters.[2] This produced two functions, one relating firing rate on every trial to movement amplitude, the other relating firing rate on these same trials to movement endpoint. In order to see which relationship described the data better, we computed the variance accounted for by the arctangent fit as (total variance−residual variance)/total variance (where variance was defined as the sum of the squared cartesian distances from the mean firing rate for all movements).

[1]Raw changes in variance accounted for can only be used as an estimate of neuronal variance if we assume that the linear regressions yield similar parameters under memory and non-memory conditions. As we show below, this is the case for this population.

[2]Note that although previous reports from this laboratory showed that linear models were often sufficient for capturing the variance in SNr neuronal firing rates, we found that during movements from lateral origins, many neurons were maximally modulated for several of the largest amplitude movements we studied (movements outside the range measured in previous studies). As a result, linear models tended to slightly over- or underestimate responses for extreme movements. In order to more accurately capture responses for large saccades, we chose sigmoidal functions for this purpose which describe nigral responses more accurately than linear functions over this range.

Finally, in order to ensure that there was no systematic effect of orbital position in addition to the spatial tuning described by our arctangent fits, we calculated the residual variance (the difference between the observed and predicted firing rates) remaining after fitting the firing rate and amplitude data with the arctangent function. We then examined the residual error for each movement as a function of the initial position of the eye for that movement by performing a linear regression for all movements. The slope of the regression line gave a quantitative measure of whether there was a systematic change in firing rate as a result of changes in orbital position.

Peri-stimulus time histograms

For some neurons, peri-event time histograms were also generated to examine the temporal relationships between modulations in neuronal activity, variance in neuronal rate, and significant task events. For each peri-event time histogram we averaged the firing rate of the neuron across many similar trials into 25 ms bins and plotted these averages as a function of time. For each neuron, five histograms of 400 ms duration were generated from memory saccade trials, centered, respectively, on the time when the monkey aligned gaze with the central LED, the time when the eccentric LED was illuminated, the time when the eccentric LED was extinguished (the beginning of the memory interval), the time when the saccade required for reinforcement began, and the time when reinforcement was delivered. For the activity of neurons during saccades from multiple origins, similar trials were defined in two different ways. First, we sorted the movements by where they started, and averaged together the responses of the neuron for movements of amplitude similar to the best movement of the neuron. Second, we selected the responses of the neuron for movements with endpoints similar to the endpoint of the best movement of the neuron. For all histograms, in addition to plotting average firing rate during each bin, we also plotted the standard deviation and standard error of the mean for each bin, which allowed both the trial-to-trial variance in firing rate and the accuracy of the mean estimates to be examined.

Population analyses

Variance

In order to determine whether our population of nigral response fields showed a systematic increase or decrease in overall variability, we plotted, for each neuron during each interval, the variance accounted for by our linear fits during memory trials against the variance accounted for during delayed saccade trials.

Response fields

We analyzed the response fields for evidence that a memory interval introduced a systematic change in response field structure by producing a population-level comparison of the responses of SNr neurons during the memory saccade task and the delayed saccade task. For each neuron during each interval, we extracted the average neuronal firing rate, the steepness of the neuronal tuning function, and the best direction for the neuronal tuning function. These parameters provide good estimates of the overall magnitude of activity modulations, the degree to which these modulations are linearly related to horizontal and vertical saccade amplitude, and the movement directions associated with the most significant modulations (for details, see Handel and Glimcher 1999). To compare the overall magnitude of SNr responses, for each neuron we plotted the average peri-saccadic percent change in firing rate from baseline during memory saccade trials as a function of the average peri-saccadic firing rate during delayed saccade trials. To examine the degree of spatial tuning in SNr responses, for each neuron we plotted the steepness of the neuronal tuning during memory saccade trials as a function of the steepness of the neuronal tuning during delayed saccade trials. To compare the best directions for each neuron, we subtracted the direction of the slope of the response field during memory saccade trials from the direction of the slope of the response field during delayed saccade trials. This directional difference was then plotted as a histogram and used to determine the circular correlation coefficient between the orientations of the regression planes during the two tasks (Batschelet 1981). Finally, if there was a significant correlation (by Rayleigh test), the difference was computed as the mean angle of the directional difference.

Orbital position

In order to compare whether the amplitude or endpoint was better correlated with firing rate for all of the neurons in our population, we computed a goodness-of-fit ratio which compared the amount of variance accounted for by both arctangent fits. This value was the sum of the variance accounted for by the amplitude function and the endpoint function, divided by the difference between the variance accounted for by each function. This ratio could run between −1 and 1, where values greater than zero indicated that amplitude accounted for more variance in the firing rate, and values less than zero indicated the converse.

Results

Orbital position related activity

Previously, we demonstrated that SNr neurons could be sorted into four classes, two of which show a pause in tonic spike rate prior to saccades and two of which burst prior to saccades (Handel and Glimcher 1999). In the following analyses, we follow this general convention, presenting data on a typical saccade-related pausing neuron and a typical saccade-related bursting neuron separately.

We recorded from 30 neurons while monkeys performed at least 200 trials (mean: 273 trials, SD:63 trials) of the delayed saccade task which included movements from 3 different initial eye positions.

Single neuron analyses

Pausing neuron

Figure 2 shows PSTHs aligned to the time of movement onset for a single pausing cell from this population. Figure 2A represents the responses during movements with an amplitude and direction similar to that which elicited the maximal response from the neuron. However, they have been separated into two groups based on the orbital position at the beginning of the movement. Note that the neuronal responses appear to be similar regardless of the origin from which these movements were initiated. Irrespective of the origin of the movement or the final orbital position, the firing rate of the neuron is reduced around the time of the movement. In contrast, Fig. 2B shows the responses of the same neuron for movements which have the same final orbital position, again

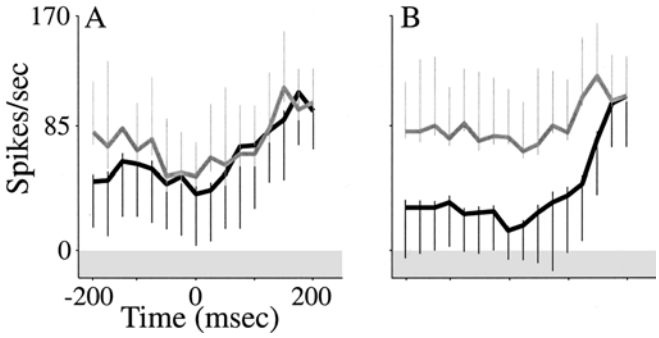

Fig. 2A, B Peri-event time histograms for a pausing neuron. Average activity, standard deviation and standard error plotted aligned to movement onset. **A** Activity during saccades similar in amplitude to the movement which elicited the best response from the neuron. Movements from the left in *black,* movements from the right in *grey.* **B** Activity during saccades with similar endpoints to the movement which elicited the best response from the neuron. Movements to the left hemifield in *black,* movements to the right hemifield in *grey*

segregated by initial orbital position. In this condition, the cell responds differently during movements from different origins. Movements from the right origin are in the direction of the cell's preferred movement, and the neuron shows a decrease in firing rate. However, movements from the left origin to the same final orbital position were made in the opposite direction, and there is little modulation in the firing rate.

A direct comparison of Fig. 3A and Fig. 3B shows that firing rate appears to be more closely correlated with movement amplitude than endpoint. These figures show the average firing rates for all movements grouped by their initial eye position, and the arctangent function explaining the greatest amount of variance in the data is shown underneath in grey. In Fig. 3A, the mean firing rates for movements of the same amplitude are quite similar for movements from all three origins. The data appear to be highly overlapping, and the fit well captures the area of steepest change in firing rate for movements from all three origins. In contrast, when plotted as a function of endpoint (Fig. 3B), the mean firing rates for movements of the same endpoint appear to be quite different.

Figure 3C and Fig. 3D show that for all movements, the firing rate of this neuron is better correlated with movement amplitude than movement endpoint. The arctangent which explained the greatest amount of variance in firing rate as a function of amplitude (Fig. 3C, plotted in grey behind the data) accounts for nearly twice as much variance in the data as the relationship between firing rate and endpoint (Fig. 3D).

There was no residual systematic effect of initial eye position on SNr firing rates which was independent of the spatial tuning of this neuron. When we performed a linear regression of the residual variance as a function of orbital position, we found no statistically significant relationship between these two quantities (slope = 0.14 spikes/s/deg, $p>0.01$).

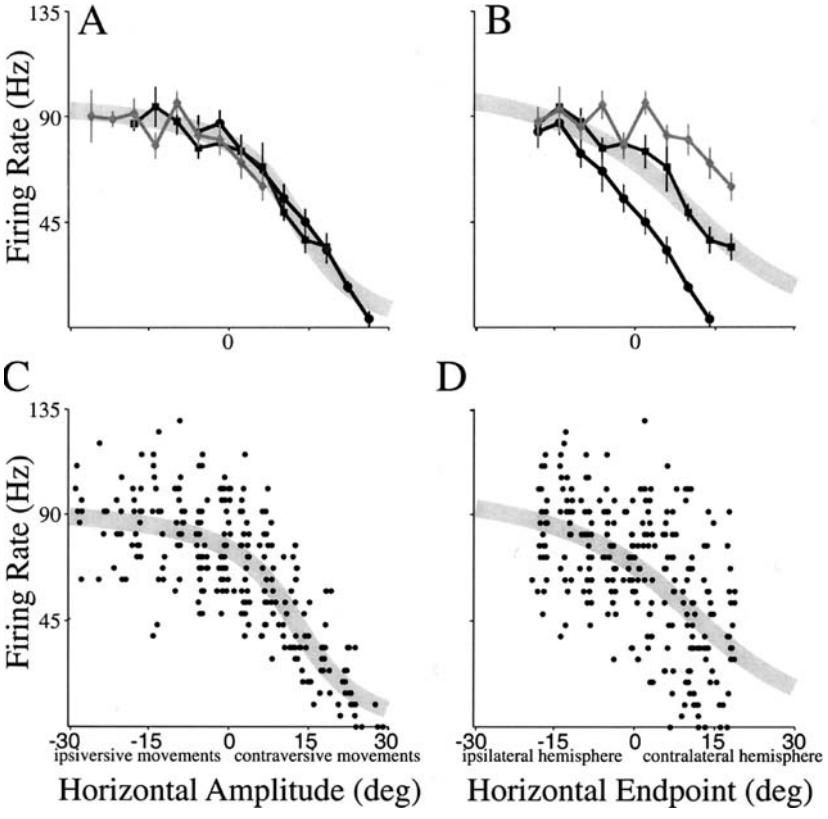

Fig. 3 **A** Mean firing rate and standard error for pausing neuron responses to movements of different horizontal amplitude. Movements from the left in *black,* movements from straight ahead in *dark grey,* and movements from the right in *light grey.* **B** Mean firing rate and standard error for the same neuron with responses grouped by horizontal endpoint. **C** Firing rates as a function of amplitudes, with the best fitting arctangent function. VAF = 64%. Firing rates as a function of endpoints. VAF = 33%

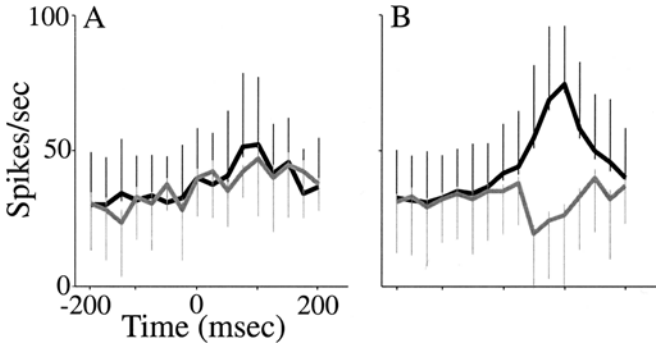

Fig. 4A, B Peri-event time histograms for a bursting neuron. **A** Activity during saccades with similar amplitudes to the movement which elicited the best response from the neuron. **B** Activity during saccades with similar endpoints to the movement which elicited the best response from the neuron

Bursting neuron

Figure 4A and Fig. 4B are PSTHs for a typical bursting neuron suggesting that, as seen for the pausing neuron, movements of the same amplitude evoke similar responses while movements with the same endpoint do not. In Fig. 5A, where the average response was drawn from movements which are all similar in amplitude, the firing rate of the neuron increases around the time of the movement, with the same level of response for movements from both origins. This suggests that orbital position has no effect on the response of the neuron during movements of similar amplitude. Figure 4B shows the response of the same neuron during movements which have the same range of endpoints. All of these responses were recorded during movements which ended in similar orbital locations, but movements from right and left origins are of different amplitudes, and elicit dramatically different responses from this neuron.

Figure 5A shows the average firing rate for each of the movements we collected separated out by origin. In this figure, points corresponding to movements having the same amplitude are largely overlapping, suggesting that the firing rate depended on movement amplitude, independent of the initial orbital position. In contrast, Fig. 5B shows points corresponding to movements with the same endpoint. In this case, the responses of the neuron during movements from different orbital positions appear to be shifted away from each other; there is no unique correlation between any endpoint and any rate of neuronal response. This further suggests that the firing rate of this neuron is systematically modulated by the movement amplitude, but not by orbital position.

In order to determine whether this general observation was consistent throughout our entire data set from this neuron, Fig. 5C and Fig. 5D show the responses of this neuron during all the movements we recorded, plotted as a function of horizontal amplitude (c) or endpoint (d). For this neuron, firing rate was much better correlated with movement amplitude than endpoint. Superimposed in grey on these data points is the function which explained the greatest amount of variance in each condition. The relationship between firing rate and movement amplitude accounts for a third more variance than the relationship between firing rate and movement endpoint.

The relationship between firing rate and amplitude accounted for more than two-thirds of the variance in our

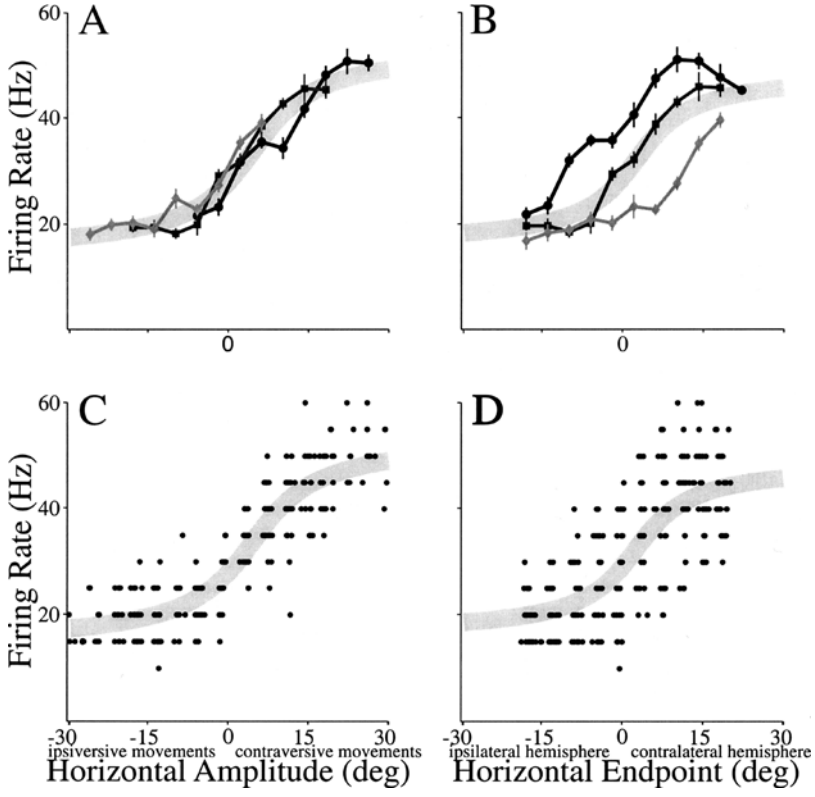

Fig. 5 **A** Mean firing rate and standard error for bursting neuron responses to movements of different horizontal amplitude. Movements from the left in *black,* movements from straight ahead in *dark grey,* and movements from the right in *light grey.* **B** Mean firing rate and standard error for the same neuron with responses grouped by horizontal endpoint. **C** Firing rates as a function of amplitudes, with the best fitting arctangent function. VAF = 82%. **D** Firing rates as a function of endpoints. VAF = 55%

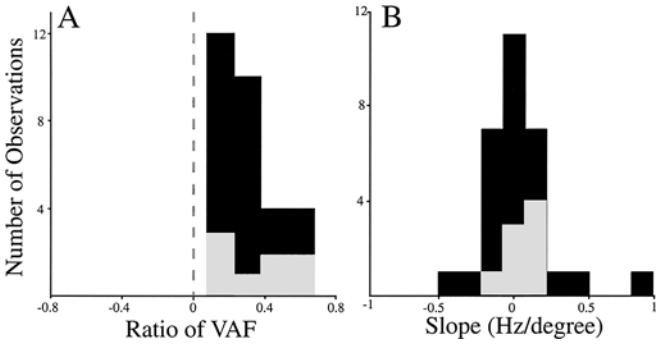

Fig. 6A, B Population statistics for all 30 neurons; pausing neurons in *black,* bursting neurons in *grey.* **A** Histogram of goodness of fit measure. Contrast ratio of variance accounted for by best fitting amplitude and endpoint arctangent functions. **B** Histogram of slopes from regressions of residual variance

observations of this neuron, and we found that there was a very minimal effect of orbital position in the remaining variance. For this neuron, all evidence suggests that firing rate was most strongly correlated with amplitude, independent of eye position. A regression line for the residual error values as a function of initial orbital position produced no meaningful relationship (slope = −0.1 spikes/s/deg, $p<0.005$).

Population analyses

When we quantitatively compared the relative effectiveness of the best arctangent fits for each cell in our population (both pausers and bursters), we found that for every neuron we studied firing rate was better correlated with movement amplitude than with movement endpoint. Figure 6A is a histogram of the goodness-of-fit measure for all of our neurons, with pausing neurons shown in black, bursting neurons in grey. For the entire population, both pausers and bursters, the variance accounted for by the amplitude fit was greater, and thus the ratio of variance accounted for was always greater than zero (mean = 0.3, SD = 0.16).

When we looked at the regression slopes for the residual variance as a function of orbital position for all of the neurons, we found that as a population, SNr neuronal responses did not appear to be systematically modulated as a function of eye position (Fig. 6B). Slopes for pausing neurons are plotted in black, bursting neurons in grey, and all appear to be clustered around zero. Although several neurons showed tiny but statistically significant slopes, and there was a single outlier at 0.8 Hz/degree, these appear to be the extremes of a distribution centered very near to zero (mean = 0.05, SD = 0.25).

Memory guided saccade related activity

We recorded from 28 SNr neurons while monkeys correctly performed at least 50 trials of both the memory saccade task (mean: 134 trials, SD: 86 trials) and the delayed saccade task (mean: 169 trials, SD: 89 trials). (An analysis of the delayed saccade task data from 26 of these neurons has been presented previously in Handel and Glimcher 1999.)

Single neuron analyses

Pausing neuron

In order to examine the activity of a single pausing neuron during our memory saccade task, in Fig. 7 we plot the planar regressions and residuals, which describe the response fields measured for this neuron, during the Visual, Movement, Memory, and Reward intervals of memory saccade trials (Fig. 7A). (As a control, all analyses were also performed on the neuronal responses

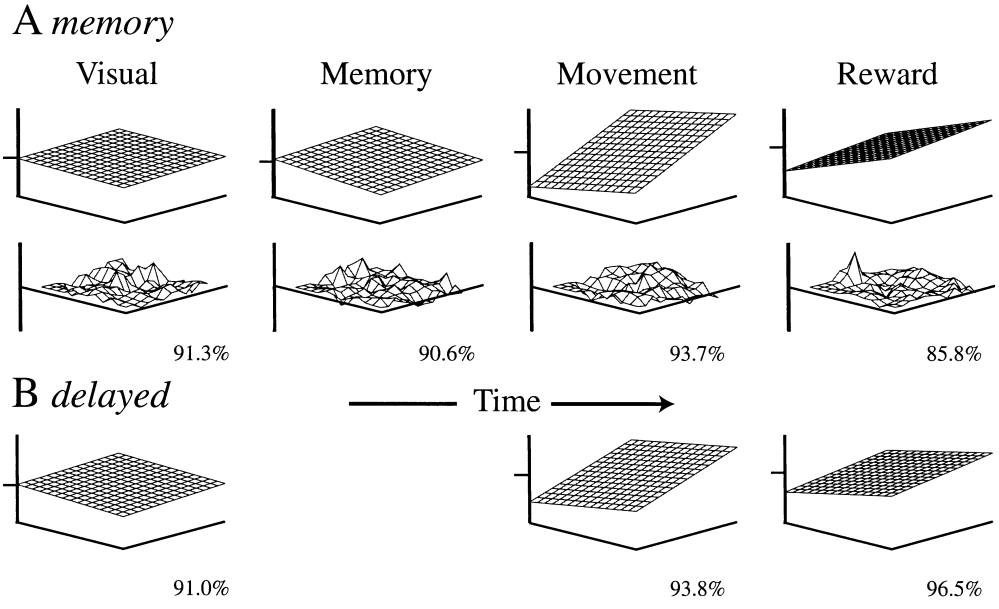

Fig. 7 **A** Response fields for a pausing neuron during memory saccade trials. Intercepts, from left to right: 85%, 57%, 23%, and 63%. Slope magnitudes: 0.27 spikes/s/deg, 0.17 spikes/s/deg, 0.63 spikes/s/deg, and 0.43 spikes/s/deg. Slope directions (uphill): 255°, 161°, 13°, and 38°. **B** Response fields during delayed saccade trials. Intercepts, from left to right: 85%, 35%, and 65%. Slope magnitudes: 0.24 spikes/s/deg, 0.61 spikes/s/deg, and 0.82 spikes/s/deg. Slope directions (uphill): 49° and 66°. For fixation interval during memory and delayed saccade trials respectively: intercept: 96% and 96%; slope magnitude: 0.22 spikes/s/deg and 0.38 spikes/s/deg; slope direction: 7° and 163°

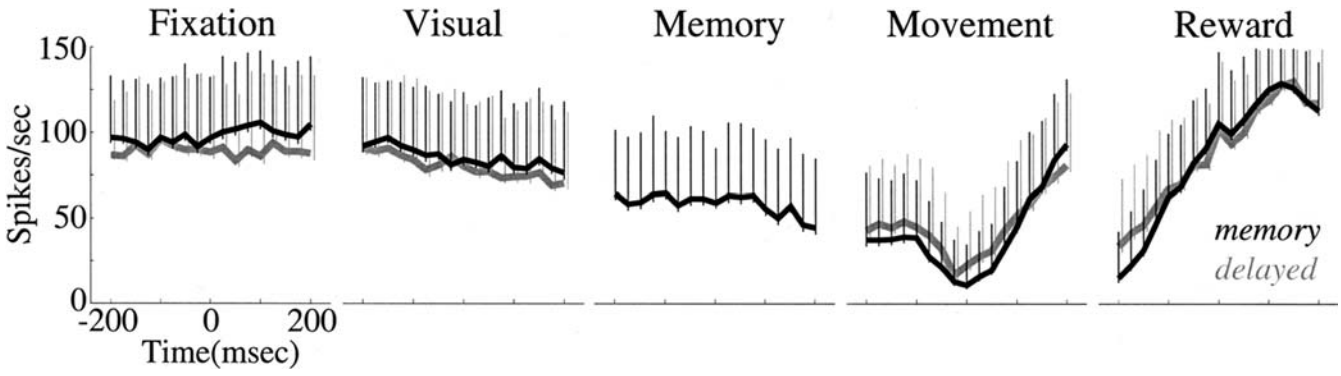

Fig. 8 Peri-event time histograms for a pausing neuron during all 246 memory saccade trials (in *black*) and 260 delayed saccade trials (in *grey*)

during the Fixation interval, but for brevity, are not shown in the figures. Results during this interval are reported in the figure legends for the interested reader.) We also show the variance accounted for by these planar fits as an estimate of the variance in neuronal rate during memory saccades. For comparison, we plot delayed saccade trial data for this same neuron (in grey, Fig. 7B).

During both tasks, the average firing rate of the neuron gradually dropped further and further below baseline during the Visual and Movement intervals and remained below baseline during the Reward interval. The size of these decreases in average rate were similar in both tasks, as was the random variance in firing rate. There appeared to be no substantial difference either in the overall variability in neuronal firing rate or in the structure of the response fields for this neuron during memory saccade and delayed saccade trials.

The response fields in Fig. 7 allowed us to compare the activity and spike rate variance of this neuron on all trials, but during only three discrete intervals. To compare neuronal activity throughout these tasks we averaged firing rates across trials to generate peri-event time histograms for the memory saccade task and computed the standard deviation and standard error of firing rate for each histogram bin (Fig. 8). In gray we plot, for comparison, data for the same neuron from delayed saccade trials. There was essentially no difference in the magnitude or timing of modulations in the average firing rate or in the firing rate variance during the two tasks. Furthermore, in the peri-event time histogram which is centered on the onset of the memory interval, the average firing rate was intermediate across the average firing rates observed after the onset of the target and before the onset of the movement and showed no systematic change in variance. For this neuron there appeared to be no significant differences between the modulations in firing rate observed on memory saccade and delayed saccade trials

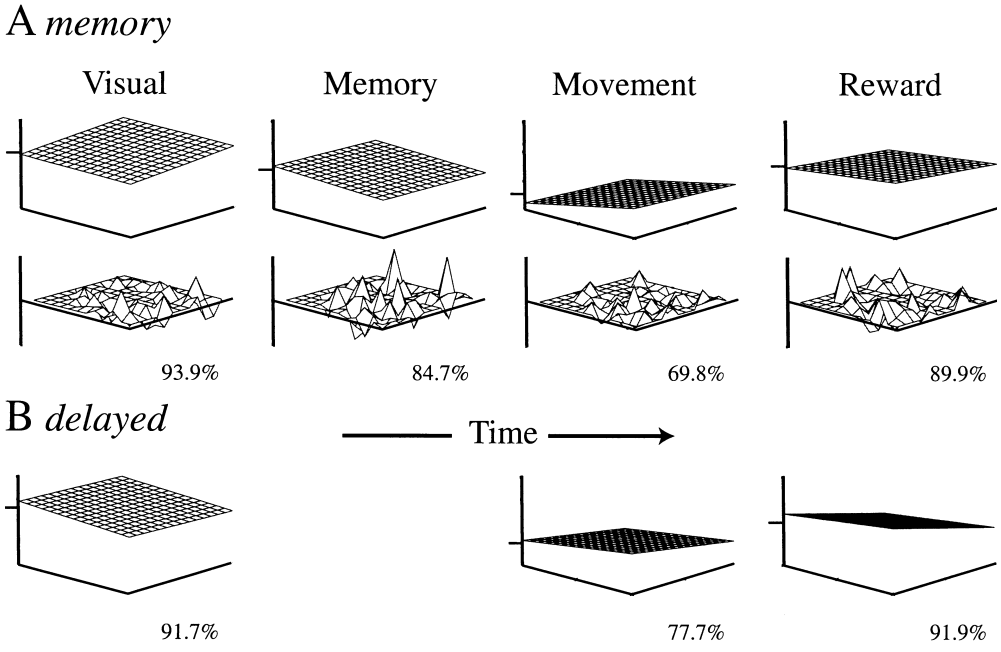

Fig. 9 **A** Response fields for a bursting neuron during memory saccade trials. Intercepts, from left to right: 102%, 98%, 122%, and 136%. Slope magnitudes: 0.21 spikes/s/deg, 0.44 spikes/s/deg, 1.93 spikes/s/deg, and 1.36 spikes/s/deg. Slope directions (uphill): 309°, 321°, 250°, and 199°. **B** Response fields during delayed saccade trials. Intercepts, from left to right: 104%, 132%, and 136%. Slope magnitudes: 0.32 spikes/s/deg, 1.42 spikes/s/deg, and 0.94 spikes/s/deg. Slope directions (uphill): 313°, 247°, and 219°. For fixation interval during for memory and delayed saccade trials respectively: intercept: 103% and 105%; slope magnitude: 0.03 spikes/s/deg and 0.10 spikes/s/deg; slope direction: 272° and 121°

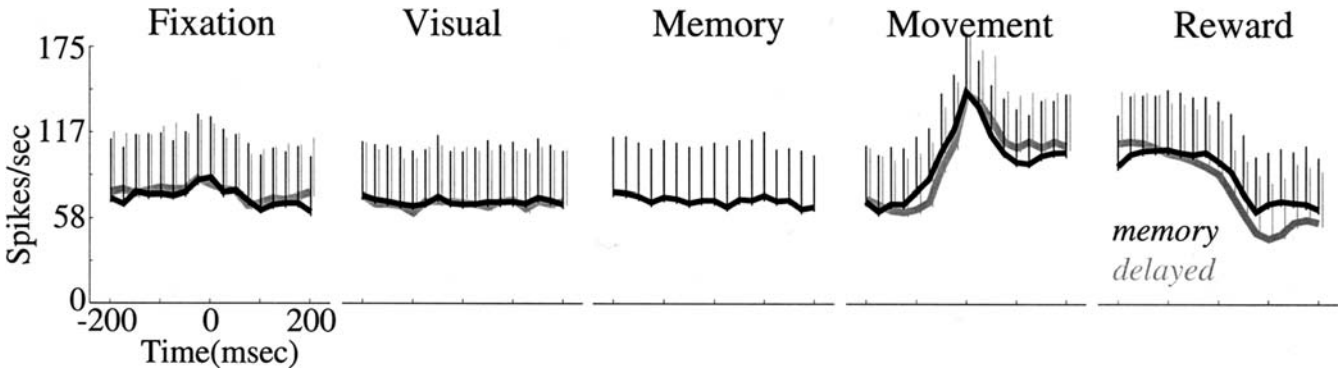

Fig. 10 Peri-event time histograms for a bursting neuron during 151 memory saccade trials (in *black*) and 144 delayed saccade trials (in *grey*) during which the eccentric LED was at least 10° above fixation

Bursting neuron

As with the pausing neurons, our population of bursting neurons showed no clear difference between delayed saccade and memory saccade trials. This was true during all of the measured intervals. Figure 9 plots the response fields of this neuron during both the memory saccade task and the delayed saccade task. For both tasks, the response fields remained flat and near baseline until the Movement interval. During the Movement interval there was no substantial difference between the response fields; for both tasks, the firing rate of the neuron increased by a similar amount, showed a similar degree of spatial tuning, with a similar orientation, and showed similar values for the variance accounted for by the planar regressions. This neuronal response, with similar variance, continued into the Reward interval for both tasks.

This pattern of results remained consistent when responses were not averaged into the canonical epochs, as seen in the PSTHs in Fig. 10. The black lines show average firing rates for this neuron during all memory saccade trials ending with large amplitude upwards movements. The grey lines show average firing rates during similar delayed saccade trials for comparison.

Population analyses

Comparison of the two tasks: response field structure

In our examination of single SNr neurons we found that some neurons responded nearly identically for both the memory and delayed saccade tasks, and some showed differences in responding across the two tasks. In order to determine whether the SNr population as a whole showed a systematic change in response field structure we compared the responses of our SNr population across the two tasks for each measured interval. We made this comparison using parameters from the planar regressions fit to the response fields of the SNr neurons: the average neuronal peri-saccadic firing rate, the steepness of the neuronal tuning function, and the best direction for the neuronal tuning function.

The plots in Fig. 11 compare the average firing rate during each interval (expressed as a percentage of

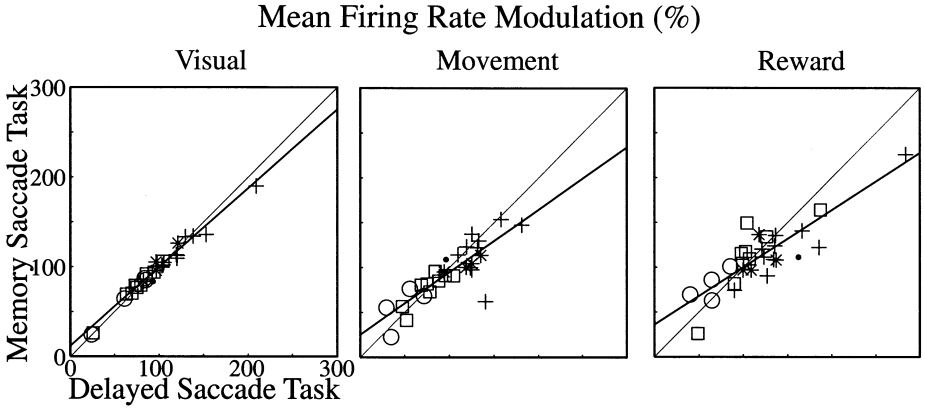

Fig. 11 A comparison of mean firing rates during memory saccade trials and delayed saccade trials for 28 SNr neurons during the Visual, Movement, and Reward intervals. Mean firing rates are estimated with the *z*-intercepts of the regression planes from the response fields and presented as a percentage of baseline. For the three intervals, correlation coefficients (*r*) were 0.99, 0.84, and 0.85, respectively; paired *t*-test: $p = 0.43$, 0.12, and 0.11, respectively. For the fixation interval, r was 0.95, and $p = 0.39$. Memory saccade cell classes (based on the classification scheme developed for delayed saccade data by Handel and Glimcher 1999): *open circles* discrete pausers, *open squares* universal pausers, *pluses* bursters, *asterisks* pause-bursters, *dot* unclassified

baseline) for all 28 neurons in our population. Each graph plots the average neuronal peri-saccadic firing rate from the planar regression for the memory saccade data as a function of the average neuronal peri-saccadic firing rate from the planar regression for the delayed saccade data. During the Visual intervals nearly all neurons fell close to the identity line (grey), indicating that there was no overall difference in average firing rates across the two tasks.

A linear regression of the mean firing rate from the memory saccade data against the delayed saccade data, in each interval, provided weak evidence for a structural change in nigral response fields. Under these conditions the regression slopes were slightly less than 1.0 (0.89, 0.70, and 0.64, for visual, movement and reward intervals, respectively), suggesting that the population of nigral saccade related neurons may be more weakly modulated during memory saccade trials than during delayed saccade trials. However, we found no significant differences between the response of the population on memory and delayed saccade trials in any interval by paired *t*-test

The results in Fig. 11 show that the overall magnitude of SNr population responses were not significantly affected by whether the monkey was performing a task requiring memory-guided saccades or visually-guided saccades. However, it is possible that the steepness of the neuronal tuning functions might have been influenced by the memory requirement of the task. Figure 12A compares the steepness of the neuronal tuning functions observed during each interval across the two tasks for all the neurons in our population. Each graph plots the magnitude of the slope of the planar regression from the memory saccade data as a function of the magnitude of the slope of the planar regression from the delayed saccade data. Note that, while there is significant scatter, there is no evidence for a consistent shift toward a steeper or shallower neuronal tuning function for memory saccade trials. In fact, there were no significant differences in neuronal tuning function slope across the two tasks for any of the three intervals (Visual, Movement, and Reward) where spatial tuning would be expected.

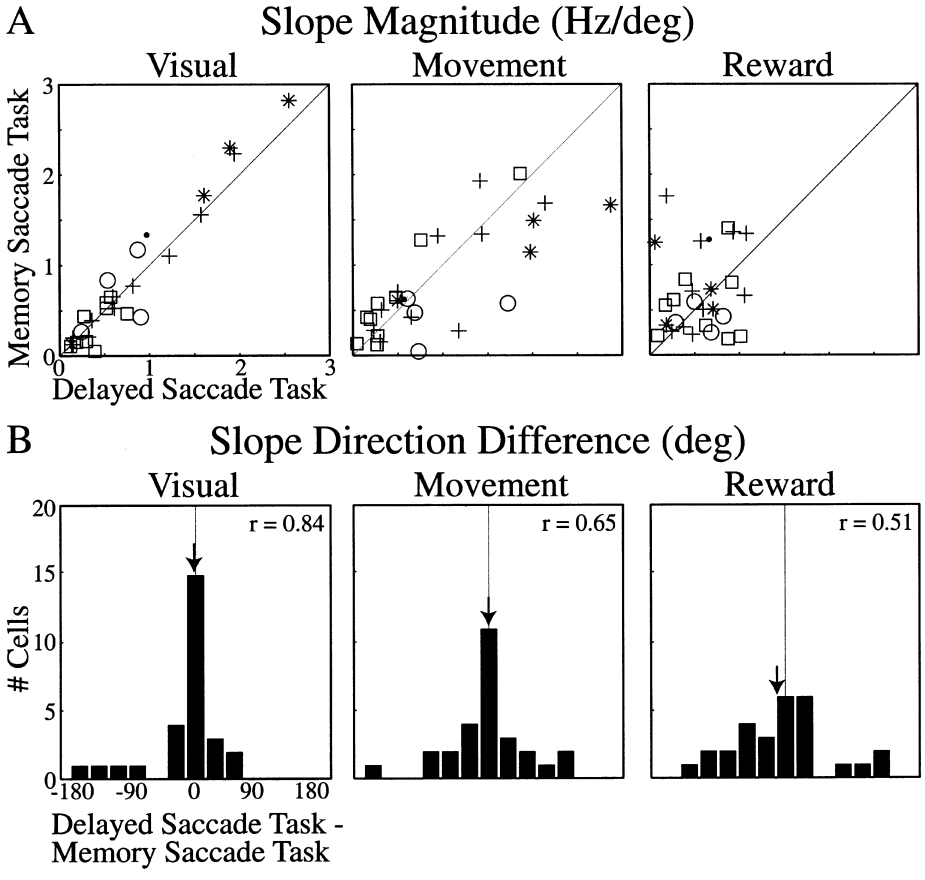

Fig. 12 **A** A comparison of the spatial tuning magnitude of neuronal responses during memory saccade trials and delayed saccade trials for 28 SNr neurons during the Visual, Movement, and Reward intervals. Spatial tuning magnitudes are estimated with the magnitudes of the regression slopes from the response fields. For the three intervals, as well as the fixation interval, correlation coefficients (*r*) were 0.97, 0.78, and 0.11, respectively; paired *t*-test: $p = 0.42$, 0.18, 0.22, respectively. For the fixation interval, *r* was 0.31, and $p = 0.01$. Delayed saccade cell classes: *open circles* discrete pausers, *open squares* universal pausers, *pluses* bursters, *asterisks* pause-bursters, *dot* unclassified. **B** Histograms of the angular difference between the directions of the regression slopes from the response fields for memory saccade trials and delayed saccade trials. For the three intervals, circular correlation coefficients (*r*) were: 0.14, 0.84, 0.65, and 0.51, respectively, and the average directional differences were −2.4°, −0.4°, and −13.0°, respectively. For the fixation interval, *r* was 0.14, and the average directional difference was −122.2°

It is also possible that, although the overall magnitude of SNr responses and the degree of spatial tuning in those responses were not affected by the memory requirement, the best direction of each neuronal tuning function was altered. To test this possibility, we compared the directions of the slopes of the planar regressions in the two tasks. For each interval we subtracted the best direction of the memory saccade regression plane from the best direction of the delayed saccade regression plane to get a measure of the difference in best direction across the two tasks. These direction differences are plotted as histograms in Fig. 12B. In addition to being correlated, the slope directions tended to be the same in both tasks: the average difference in direction between the two tasks was close to zero in the Visual, Movement, and Reward intervals. Thus, the orientation of SNr population responses was essentially unaffected by whether monkeys ran the memory or the delayed saccade task.

Discussion

Summary of results

In this report we studied the effect of eye position on the responses of SNr neurons by examining firing rates during movements from different initial orbital positions. We quantified our observations using an arctangent function to determine which variable accounted for a greater amount of the variance in the neuronal responses that we observed. For all of our neurons, both those that paused and those that burst, firing rate was better correlated with movement amplitude than final eye position. After accounting for variance in firing rate due to the spatial tuning of each neuron, we also examined the residual errors from these fits as a function of eye position. The regressions we performed showed no systematic effects of eye position across all neurons in our population. Taken together, these results suggest that SNr saccade-related neurons carry no information about the orbital position of the eye.

We studied the effect of a memory interval on nigral responses by comparing nigral activity in a pair of very similar delayed saccade and memory saccade tasks. We compared single trials during which subjects made identical movements guided by visible or remembered targets and showed no difference in neuronal response observed under these conditions. For both pausing and bursting neurons, there was no systematic difference between responses during delayed saccades and memory saccades in our tasks. Averaging the responses of multiple movements of similar amplitude and direction in the form of PSTHs also indicated that neurons responded similarly during both of these types of visual and memory guided saccades. Finally, comparing movements of a wide variety of amplitudes and directions in the form of response fields and planar fits to these response fields also showed similar responses for saccades to visible and remembered targets. In summary, the activity of saccade-related neurons in the SNr was not affected by whether the saccades were made towards visible or remembered targets in the two closely related tasks we examined.

We report here that during saccade tasks which are matched for all variables except for a memory delay, SNr neurons do not show a unique response pattern for saccades to remembered targets. This result might seem to be in conflict with the original findings of Hikosaka and Wurtz (1983c), which suggested that nigral neurons were especially active during memory saccades. However, our memory task was not identical to the one they employed. Thus, both our results and theirs might be thought of as supporting the hypothesis that SNr neuronal responses are modulated by the context in which saccades are executed. It is possible that their original results reflected differences in context, and that by eliminating those differences in our experiment, we eliminated the differences in nigral responses.

What might be the critical difference in context? One possibility is the animals' expectations of reward. Recent work by Sato and Hikosaka (2002) has shown that expectation of reward can have a significant effect on the response properties of nigral neurons. One potential source of variability between visually and memory guided saccades could be the rate at which animals were rewarded. In our experiments, animals were trained until their rates of success during the two tasks were equal. However, if, for example, in the Hikosaka and Wurtz studies, the animals performed more poorly during the memory saccade task than during the visually guided saccade task, we might expect the difference in the rate of reward to be reflected in the responses of the neurons.

In our data, we saw no difference in the neuronal responses during visual and memory guided saccades based on reward expectation, presumably since the experiments were designed to control for this variable. However, we did find that occasionally the responses of the neurons extended into the post-saccadic interval. It has been shown by Wolfram Schultz and colleagues that neurons in the substantia nigra pars compacta (SNc) respond following rewards which are unexpected. It is possible that the later responses that we have seen in SNr neurons reflect something about the animals' expectation of reward and could be used to determine whether or not a reward was expected. In the future, it would be of great interest to test this hypothesis by comparing the temporal response profiles of neurons in the SNr with those of neurons in the SNc during a task in which an animal's expectation of reward was parametrically varied.

Comparison with other saccade-related areas

These results provide data for comparison with neuronal responses in other saccade-related areas, which should yield a clearer view of how signals in the SNr might be combined with signals in other areas to generate eye movements. The SNr receives inputs from other nuclei of the basal ganglia and projects, in turn, both directly to the superior colliculus and indirectly to the frontal eye fields.

Understanding the precise kinds of information that the SNr can convey to these areas and how nigral signals differ from those sent by parietal eye movement control areas to the SC and FEF should help us to determine what role the SNr plays in saccade generation.

Our observation that neurons of the SNr show no effect of eye position on their responses suggests that SNr neurons carry signals that are in the same coordinate frame as those encoded in the FEF; no coordinate transformations would be required for communication between these areas. In contrast, the saccade-related neurons of posterior parietal cortex (Andersen et al. 1990, 1985; Andersen and Mountcastle 1983) have been shown to carry information in a multi-dimensional coordinate frame encoding information about both eye position and saccade amplitude. Projections from this area to the FEF must therefore undergo a coordinate transformation. Indeed, it has even been argued that this transformation between alternative coordinate systems is a principle function of posterior parietal cortex (Andersen et al. 1993). Our data suggest that the SNr participates in no such signal transformation.

We also found that SNr neurons show responses which did not significantly differ during very similar visually guided and memory guided saccade tasks. While many saccade-related areas have been shown to respond in a roughly similar fashion during both delayed saccade and memory saccade tasks, the apparent insensitivity of nigral activity patterns to this variable appears fairly unique. Activity in the SC and FEF, for example, appears to be weaker during memory saccade tasks than during delayed saccade tasks, although this change in response magnitude may be attributable to changes in accuracy, velocity, or endpoint (cf. White et al. 1994; Stanford and Sparks 1994; Gnadt et al. 1991). In any case, these data suggest that SNr activity during some classes of tasks that employ memory intervals is surprisingly stable, although this may not be true for all types of memory interval tasks.

Hikosaka and Wurtz (1985b) hypothesized that the projections from the SNr to the SC and indirectly to the FEF provided an important control mechanism for the generation of saccades, one which was largely independent of the parietal mechanism for saccade control. They suggested that these projections tonically inhibited the saccade generating circuitry of the SC, and that pauses in SNr neuron firing rate resulted in a release from inhibition in the SC which allowed saccade execution. The results presented in this paper largely support this hypothesis; unlike parietal saccade-related neurons, the firing rates of SNr neurons encode information about movement amplitude irrespective of eye position; nigral output around the time of operantly conditioned saccades, those guided by a visible target or a remembered target location, would be appropriate for driving the activity observed in downstream oculomotor structures.

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