Activity of the Brain Stem Omnipause Neurons During Saccades Perturbed by Stimulation of the Primate Superior Colliculus

NEERAJ J. GANDHI[1–3] AND EDWARD L. KELLER[2,3]
[1]*Graduate Group in Bioengineering, University of California, San Francisco 94143;* [2]*Graduate Group in Bioengineering, University of California, Berkeley 94720; and* [3]*The Smith-Kettlewell Eye Research Institute, San Francisco, California 94115*

Gandhi, Neeraj J. and Edward L. Keller. Activity of the brain stem omnipause neurons during saccades perturbed by stimulation of the primate superior colliculus. *J. Neurophysiol.* 82: 3254–3267, 1999. Stimulation of the rostral ~2 mm of the superior colliculus (SC) during a large, visual target-initiated saccade produces a spatial deviation of the ongoing saccade and then stops it in midflight. After the termination of the stimulation, the saccade resumes and ends near the location of the flashed target. The density of collicular projections to the omnipause neuron (OPN) region is greatest from the rostral SC and decreases gradually for the more caudal regions. It has been hypothesized that the microstimulation excites the OPNs through these direct connections, and the reactivation of OPNs, which are normally silent during saccades, stops the initial component in midflight by gating off the saccadic burst generator. Two predictions emerge from this hypothesis: *1*) for microstimulation triggered on the onset of large saccades, the time from stimulation onset to resumption of OPN discharge should decrease as the stimulation site is moved rostral and *2*) the lead time from reactivation of OPNs to the end of the initial saccade on stimulation trials should be equal to the lead time of pause end with respect to the end of control saccades. We tested this hypothesis by recording OPN activity during saccades perturbed by stimulation of the rostral ~2 mm of the SC. The distance of the stimulation site from the most rostral extent of the SC and the time of reactivation with respect to stimulation onset were not significantly correlated. The mean lead of reactivation of OPNs relative to the end of the initial component of perturbed saccades (6.5 ms) was significantly less than the mean lead with respect to the end of control (9.6 ms) and resumed saccades (10.4 ms). These results do not support the notion that the excitatory input from SC neurons—in particular, the fixation neurons in the rostral SC—provide the major signal to reactivate OPNs and end saccades. An alternative, conceptual model to explain the temporal sequence of events induced by stimulation of the SC during large saccades is presented. Other OPN activity parameters also were measured and compared for control and stimulation conditions. The onset of pause with respect to resumed saccade onset was larger and more variable than the onset of pause with respect to control saccades, whereas pause end with respect to the end of resumed and control saccades was similar. The reactivated discharge of OPNs during the period between the end of the initial and the onset of the resumed saccades was at least as strong as that following control movements. This latter observation is interpreted in terms of the resettable neural integrator hypothesis.

INTRODUCTION

A quick shift of the visual axis of orientation is produced by generating rapid eye movements called saccades. Excitatory burst neurons (EBNs) in the paramedian pontine reticular formation (PPRF) of the brain stem issue a saccadic pulse signal in the form of a velocity command necessary to execute the appropriate size saccade. The activity of these cells occurs in antiphase with the omnipause neurons (OPNs), which are organized in a columnar fashion within the nucleus raphe interpositus on the midline of the brain stem within the PPRF (Büttner-Ennever et al. 1988). The OPNs discharge at a constant rate during fixation and suppress activity during all saccades (Cohen and Henn 1972; Keller 1974; Luschei and Fuchs 1972), where the suppression is at least partially due to an inhibitory input from the pontine burst region (Kamogawa et al. 1996). Keller (1974) proposed that the OPNs exert a powerful inhibitory input onto the EBNs and hence act to *gate* the saccadic pulse generator. This connection, which has been shown to exist in the cat (Nakao et al. 1980), prevents the EBNs from discharging except during rapid eye movements, when the OPNs are silent.

Additional support for the gate hypothesis comes from studies that stimulated the OPNs during ongoing movements (Keller 1977; King and Fuchs 1977). The microstimulation produced interrupted saccades—the ongoing movements stopped in mid-light but resumed shortly after stimulation offset and terminated near the target position. This finding suggests that the stimulation reactivated the suppressed OPNs, which in turn inhibited the ongoing activity in the EBNs.

Superior colliculus interactions with omnipause neurons

The superior colliculus (SC) projects extensively to the OPNs (Langer and Kaneko 1984, 1990; Raybourn and Keller 1977). In particular, the density of projections is greatest from the rostral SC and decreases gradually for more caudal regions (Büttner-Ennever and Horn 1994; Gandhi and Keller 1997a; Paré and Guitton 1994a). These results have been used to support the hypothesis that fixation neurons in the rostral pole of the SC—also termed the fixation zone (Munoz and Istvan 1998; Munoz and Wurtz 1995b; Munoz et al. 1993)—maintain fixation and suppress saccade generation by exciting the OPNs (Munoz and Guitton 1989, 1991; Munoz and Wurtz 1993a). It has been proposed further that this neural pathway re-excites the OPNs when the rostral pole of the SC is stimulated during large eye movements, reportedly producing interrupted saccades like those observed after stimulation of the OPN region (Munoz and Wurtz 1993b).

Gandhi and Keller (1999) compared the metrics of saccades

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perturbed by stimulation of sites within the rostral pole (fixation zone), more caudal areas of the SC (saccade zone), and the OPN region. The analyses demonstrated that saccades disrupted by stimulation of the fixation zone more closely resembled colliding saccades (Schlag-Rey et al. 1989) produced by stimulation of the caudal SC and were significantly different from interrupted saccades observed after stimulation of the OPN region. The most striking difference was a stimulation-induced deviation from the control (nonstimulated) spatial trajectory before the time that the movement stopped in midflight. These spatial redirections were not found for saccades interrupted by stimulation in the OPNs. Nevertheless these results do not discount the importance of excitatory SC projections to the OPNs because the stimulation-induced redirection of saccades may have resulted from current spread to the visuomotor burst neurons in the dorsal intermediate layers of the rostral SC and/or to the buildup neurons located caudal to the fixation zone. In other words, the ongoing saccade may have stopped, subsequent to the observed deviation in its spatial trajectory, because fixation neurons in the rostral pole of the SC were activated by microstimulation and in turn reactivated the OPNs. If this was the case, the observation is not limited to just fixation neurons in the rostral pole of the SC but instead extends to other cells, probably buildup neurons, located in the rostral, ~2 mm of the SC; stimulation of this larger region at the onset of 30° saccades also produces perturbed eye movements with initial and resumed components, and in between these two components, the eyes are stationary in the orbit for various intervals (Gandhi and Keller 1999). Indeed, it has been demonstrated that a significant number of connections exist between the SC and the OPNs even as far caudal as the 2-mm mark (Gandhi and Keller 1997a). Therefore the goal of this project was to study the discharge properties of OPNs during saccades perturbed by stimulations in the rostral ~2 mm of the SC. We measured the timing of pause onset and end with respect to several saccadic events and compared these values between stimulation and control trials. Also, we separately analyzed truncated saccades—trials in which the initial saccade ended grossly short of the desired target location and a resumed saccade was not generated.

Resettable neural integrator

The theoretical underpinning for much of our understanding of the saccadic eye movement system stems from a seminal model that proposed a specific local feedback neural circuit within the brainstem regions relevant for saccade control (Robinson 1975; Van Gisbergen et al. 1981). These authors used an efference copy of eye position in orbital coordinates, provided by a neural circuit they called the oculomotor integrator, to generate the error signal in their model. However, later evidence suggested that the feedback comes from an integrator that is reset at the end of each movement and, thus provides an eye displacement signal (Jürgens et al. 1981; for a review, see Moschovakis and Highstein 1994).

Recent experiments have suggested that the resettable neural integrator decays to zero with a time constant of ~50 ms (Kustov and Robinson 1995; Nichols and Sparks 1995). However, the properties of the resettable neural integrator are not observed during saccades interrupted by stimulation of the OPNs (Keller et al. 1996), saccades to double step targets (Goossens and Van Opstal 1997), and corrective saccades (Brown et al. 1997). Models that simulate the resettable neural integrator properties have had to use several nonlinear components that have not yet been identified (Brown et al. 1997). Alternatively, the apparent decay in the efference eye displacement signal observed by Nichols and Sparks (1995) and Kustov and Robinson (1995) may not reflect the processes of a resettable integrator; it can equivalently be described in terms of a damped internal representation of eye position, temporally aligned to saccade onset (Dassonville et al. 1992; Dominey et al. 1997; Schlag et al. 1998).

Yet another proposal suggests that the integrator in the local feedback pathway may be reset instantaneously (Dominey et al. 1997; Moschovakis 1994). In a theoretical evaluation, Moschovakis (1994) used the resumption of activity in OPNs to signal saccade end and instantaneously zero the resettable neural integrator. Our experimental approach—to record OPN activity during saccades perturbed by SC stimulation—provided an experimental test of the Moschovakis hypothesis. We measured OPN activity during the interruption period between the initial and resumed components on stimulation trials and compared the responses of presaccade and postsaccade firing rates. Similarly, OPN discharge after truncated saccades was studied. We then evaluated the hypothesis that the resumption of OPN activity resets the integrator.

A preliminary version of this study has been reported previously (Gandhi and Keller 1997b).

METHODS

Two juvenile, male, *Macaca mulatta* monkeys were used for this study. The experiments involved recording eye movements and neural activity from omnipause neurons while stimulating SC sites in the deeper layers to perturb ongoing saccades. All experimental protocols were approved by the Institute Animal Care and Use Committee at the California Pacific Medical Center and complied with the guidelines of the Public Health Service policy on Humane Care and Use of Laboratory Animals.

Information on surgical preparation, training procedure, experimental setup, behavioral paradigms, and data analysis have been detailed elsewhere (Gandhi and Keller 1999). Hence, only additional and relevant methodology will be presented here. Each animal had two chambers implanted on its skull, one allowed access to the superior colliculus and the other provided an approach into the pons. Before use, each chamber was opened and thoroughly cleaned under aseptic conditions. A guide tube was first used to penetrate into the dura in the OPN chamber. Next, a tungsten microelectrode (Frederick Haer) of 0.5–1.5 MΩ impedance, tested at 1 kHz, was lowered through the guide tube via a hydraulic drive system until the center of the omnipause region was encountered, a location determined by the unique discharge characteristics of these neurons during saccades (Cohen and Henn 1972; Keller 1974; Luschei and Fuchs 1972).

A similar procedure was performed for the SC chamber. A microelectrode was lowered until the superficial layers of the SC were located, identified by "swishes" heard on the audio monitor as the eyes scanned the visual field. The penetration was continued further for an additional 2.0–2.5 mm to place the tip of the electrode in the deeper layers of the SC. For the remainder of the experiment, this SC site was stimulated to perturb saccades while single OPNs were recorded with the other microelectrode.

Both behavioral and experimental conditions have been detailed elsewhere (Gandhi and Keller 1999). Briefly, the fixed vector saccade (FVS) for the SC site was determined first. Next, the monkeys were required to execute delayed, memory-guided saccades to targets

flashed at 30° eccentricities in one of several directions. Neural activity of the OPNs was recorded during the saccade task. On most blocks of data collection, stimulation of the SC site was triggered on saccade onset on randomly selected 50–75% of the trials. Stimulation currents and train durations to induce perturbations typically ranged from 10 to 25 μA and 10 to 35 ms, respectively. The stimulation frequency usually was kept constant at 400 pps.

Data collection

Horizontal and vertical eye position and velocity measurements were sampled by a 12-bit data acquisition card at 1 kHz and stored on computer disk. Radial eye position and velocity were computed off-line by the Pythagorean theorem. The amplified potentials from omnipause neurons were passed through an electronic window discriminator using both amplitude and time constraints to isolate a particular cell. The spike count numbers, the output of the discriminator, were sampled at 1 kHz and stored in register with the analogue data at each millisecond.

Measuring neural data while electrically stimulating another site in the brain produces a shock artifact in the recording, potentially corrupting the output of the electronic window discriminator even for well-isolated neurons. The method of Keller and Edelman (1994) was used to minimize the number of false spikes introduced in the counts during the period of stimulation. Briefly, a second A-D card was programmed to sample the raw neural data at 20 kHz and store the data in temporal register with the output of the spike discriminator sampled at 1 kHz. The temporally registered raw neural data and spike counts were examined off-line to detect errors in the performance of the electronic window discriminator. When discrepancies existed, an operator manually corrected the spike count records before any analyses were performed on the data.

For graphic illustrations (Figs. 1 and 2), the spike trains were converted into spike density waveforms by convolving each spike train with a Gaussian (σ = 4 ms) (Richmond et al. 1987).

RESULTS

The goal of this study was to quantify the response of OPNs during saccades perturbed by SC stimulation. In particular, an analysis of the timing and firing rate of OPN activity associated with the perturbation, which momentarily deviated and then stopped the eyes in midflight, was the primary focus. Data were collected from two monkeys (*BZ* and *HB*), of which one (*BZ*) was used in the experiments reported in the previous study (Gandhi and Keller 1999). In total, 35 OPNs were isolated. Sufficient data to allow quantitative analyses of initial and resumed components were available on 28 neurons, whereas data during truncated saccades–stimulation trials without resumed movement–were available for only 16 of these neurons. For *monkey BZ* we recorded one, three, and four OPNs each for five, four, and one SC sites, respectively, making a total of 21 neurons from 10 different stimulation sites within the SC. For *monkey HB*, we analyzed two and five OPNs from a total of two SC sites, summing to seven neurons.

The type of saccadic perturbation observed after stimulation of the deep intermediate layers of the SC was a function of the stimulation site and the targeted saccade direction relative to the FVS direction for the stimulation site (Gandhi and Keller 1999). Specifically, stimulation of any site within the rostral ~2 mm (<10° amplitude horizontal meridian) of the SC during a saccade to a flashed target at a 30° eccentricity stopped the initial trajectory, typically after some spatial redirection. In a majority of the trials, a resumed saccade, which brought the eyes near the target location, was observed. If the stimulation was applied caudal to the ~2 mm mark, only one saccade was observed when the directions of the intended saccade and FVS were similar, and this saccade was accurate. Therefore for the current manuscript, we limited our analyses to OPN response during saccades perturbed by stimulation of the rostral ~2 mm of the SC.

Preliminary analysis indicated that the timing and activity of OPN neurons were similar during control saccades in all directions. Similar observations have been reported previously (Everling et al. 1998; Fuchs et al. 1991; but also see Paré and Guitton 1994b). Therefore saccades to 30° target eccentricities were pooled from all directions, and the combined results are displayed and quantified in the ensuing illustrations.

Figure 1 illustrates the behavior of a typical OPN. The randomly interleaved control and stimulation trials were identified and are illustrated separately. The raster plot of individual trials, the mean of the spike density waveforms and each saccade's radial amplitude trace to 30° target eccentricity, all aligned on saccade onset, are shown in the *top*, *middle*, and *bottom panels*, respectively. The FVS evoked from the SC stimulation site was 2.4@354° (the notation used henceforth to represent a change in amplitude@direction).

Before presenting the quantitative analyses on the saccade-related pause parameters around initial and resumed saccade events, we first make a qualitative assessment of OPN discharge aligned on the onset and end of initial and resumed saccades. Figure 2 shows this data for three different OPNs, recorded for stimulation applied at three different SC sites. Figure 2*A* shows a temporal representation of a perturbed saccade; *B–D* graph raster plots for the three OPNs and *E* plots the averaged spike density curves for each cell. The four columns in *B–E* represent data aligned on different saccade events. These three OPNs, like all OPNs in our sample, suppressed activity during control saccades as well as the initial and resumed components of the perturbed eye movements. They typically resumed discharge in between the two saccades, especially if the *interruption period*—the duration beginning when the initial component velocity dropped below threshold and ending at the onset of the resumed saccade—was long enough to completely stop the eyes in orbit.

Timing of pause parameters

Now we consider the timing of the OPN pause onset and activity resumption during control and stimulated trials. Pause onset with respect to saccade onset and pause end with respect to saccade end were determined for the single saccades in control trials, both initial and resumed components of stimulated trials and, when available, for truncated saccades of stimulated trials. The pause parameters were determined from the spike train recorded on each trial and are illustrated on the schematics in Fig. 3. Pause onset, measured with respect to saccade onset, was the time of last spike observed around movement initiation. Pause end, determined with respect to saccade end, was the time of the first spike occurring around saccade end. For both measures, negative values indicated that the neural event preceded the saccade event. Note that the absence of a resumed saccade on stimulation trials results in truncated movements (Fig. 3*C*), the total amplitude of which is

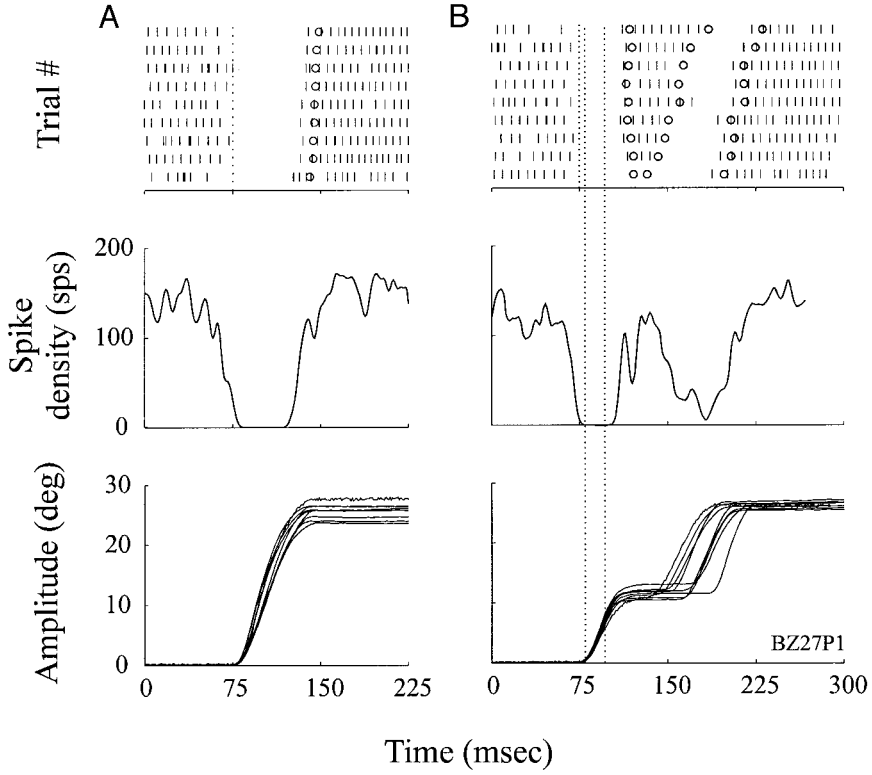

FIG. 1. Discharge characteristics of an individual omnipause neuron (OPN) during control (*A*) and stimulation (*B*) trials. *Top*: raster plots of individual trials where each vertical mark represents an action potential. All trials are aligned on saccade onset (· · ·). For each trial, ○ in *A* marks the end of the control saccade, and the 3 ○ in *B* indicate, from *left* to *right*, the end of the initial component, and the onset and end of the resumed saccade. *Middle:* each spike train was converted into a spike density function (σ = 4 ms) (Richmond et al. 1987). Average of these waveforms. *Bottom*: eye movements corresponding to the trials in the raster plot. · · · in *B* mark, from *left* to *right*, stimulation onset and offset.

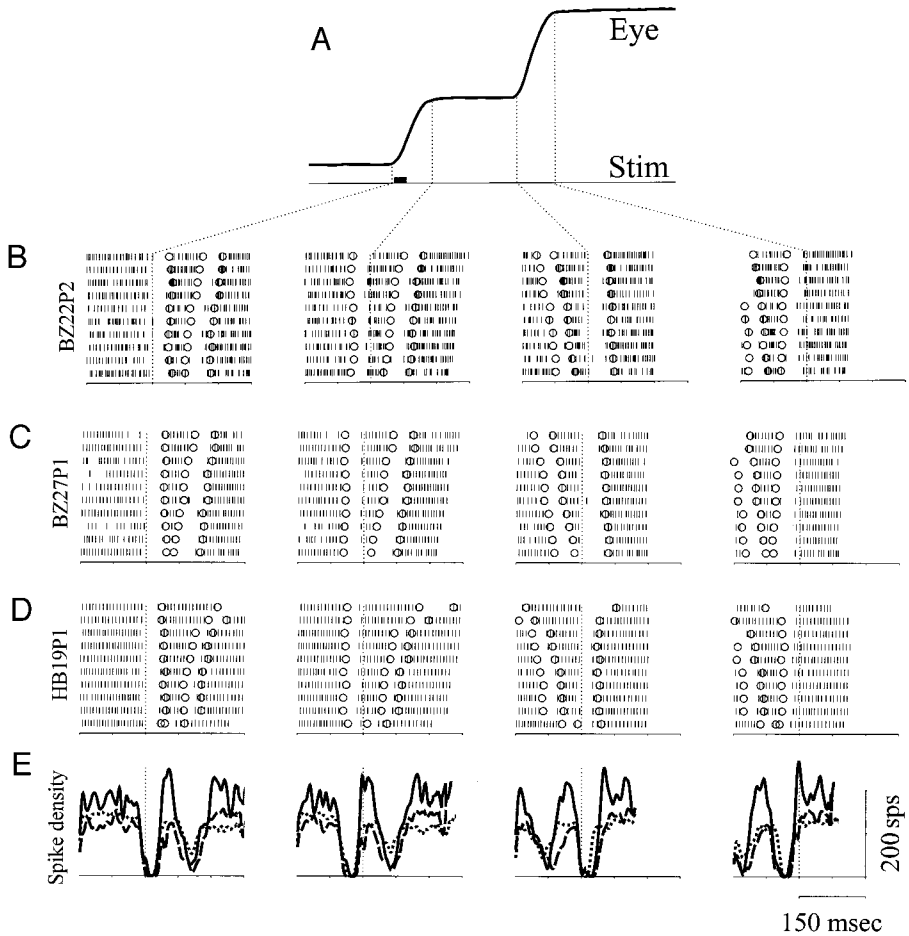

FIG. 2. Discharge characteristics of 3 OPNs, aligned on different saccade events. A temporal representation of a saccade perturbed by stimulation of the superior colliculus (SC) is illustrated in *A.* Four saccade events (· · ·) are, from *left* to *right*, the onset and end of the initial component and the onset and end of the resumed movement. Microstimulation was triggered on saccade onset. *B–D*: raster plot of 3 OPNs when stimulation was delivered to 3 different SC sites. Stimulation-evoked saccades from these 3 sites were 1.1@339° (*B*), 2.4@354° (*C*), and 8.0@190° (*D*). Trials are sorted in order of increasing interruption duration (I_{dur}; see Fig. 3). *E*: averaged spike density functions overlaid for the 3 neurons. —, - - -, and · · · , OPNs bz22p2, bz27p1, and hb19p1, respectively. *Left*: raster plots are aligned on initial saccade onset (· · ·). Three ○ denote, from *left* to *right*, initial saccade end and the onset and end of the resumed component. For trials with long I_{dur} (e.g., *top trial* in *D*) the end of the resumed component and the OPN activity thereafter fall beyond the range of plotted time scale and, therefore are not shown. *Middle left*: raster plots are aligned on initial saccade end (· · ·). Three ○ mark, from *left* to *right*, initial saccade onset, and the onset and end of the resumed component. *Middle right*: raster plots are aligned on resumed saccade onset (· · ·). Three ○ represent, from *left* to *right*, the onset and end of the initial component, and the end of the resumed saccade. *Right*: raster plots are aligned on resumed saccade end (· · ·). Three ○ from *left* to *right*, the onset and end of the initial saccade, and the onset of the resumed component. In *right* and *middle right*, the realignment often placed several saccade events on trials with long I_{dur} beyond the range of the plotted time scale and, therefore the corresponding circles and OPN activity are not illustrated.

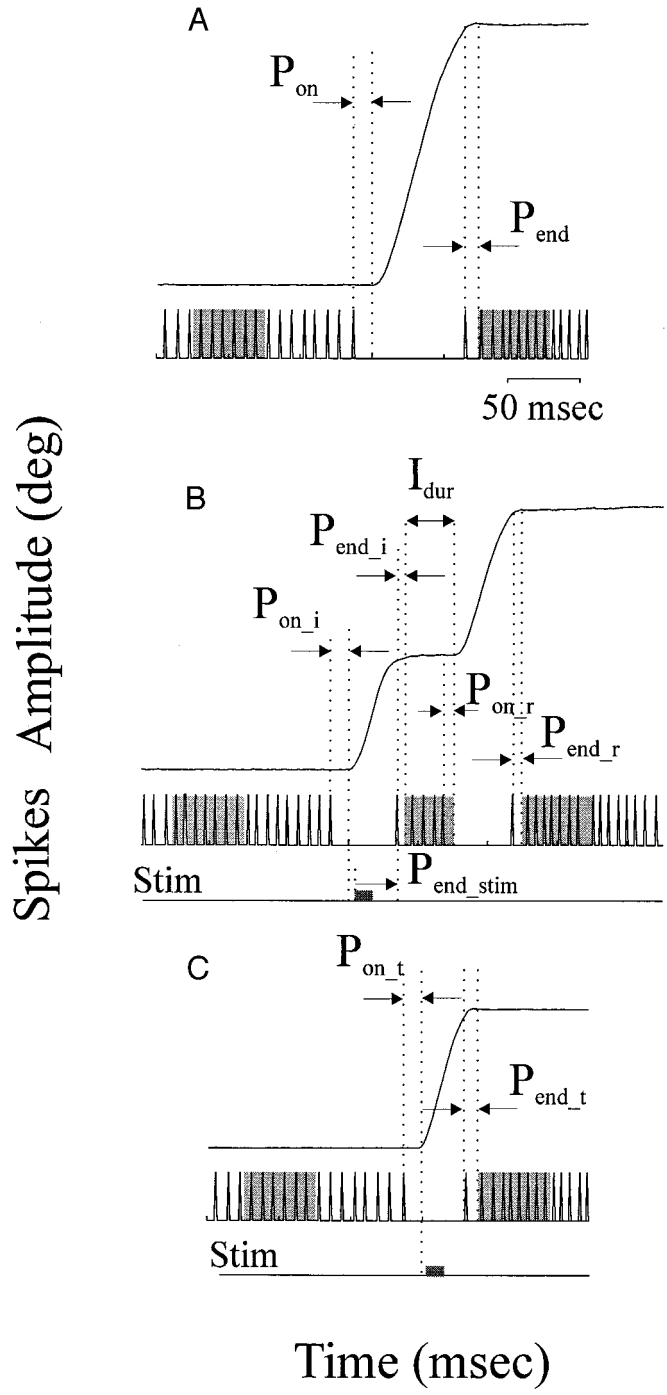

FIG. 3. Schematic to illustrate the parameters of OPN response used in subsequent analyses for control saccades (*A*), stimulation trials with initial and resumed components (*B*), and stimulation trials producing truncated movements (*C*). *Discharge rate measures* are indicated by the shaded regions: discharge rate before saccade onset (control and all stimulation trials); discharge rate after the end of control, resumed and truncated saccades; and discharge rate during the interruption period (I_{dur}) for stimulation trials with a resumed component. *Pause timing parameters* relate the temporal properties of the spike train to different aspects of the eye movement: pause onset with respect to saccade onset (P_{on}, P_{on_i}, and P_{on_t}); pause onset with respect to resumed saccade onset (P_{on_r}); pause end (resumption of OPN activity) with respect to end of control saccades (P_{end}); pause end with respect to offset of initial and resumed saccade end (P_{end_i} and P_{end_r}); pause end with respect to end of truncated saccades (P_{end_t}), and pause end with respect to stimulation onset (P_{end_stim}).

far smaller than the magnitude of control saccades to the same target (Fig. 3*A*).

Figure 4 plots the distribution of mean pause onset time with respect to saccade onset for all OPNs. The OPNs typically stopped their tonic activity before saccade onset, and because saccade onset led stimulation onset, all trials from control and stimulation conditions were pooled together to determine the distribution shown in Fig. 4*A*. We observed that mean ± SD pause onset with respect to saccade onset, averaged across the 28 OPNs, was −18.9 ± 9.4 ms. The number of saccades averaged for each OPN ranged from 15 to 160 (mean = 35). The mean pause onset with respect to the onset of resumed saccades during stimulation trials (P_{on_r}; Fig. 4*B*) was −22.4 ± 9.0 ms. The number of saccades averaged for each OPN ranged from 4 to 42 (mean =16). For each neuron, the mean P_{on_r} (Fig. 4*B*) was subtracted from the analogous measure for control saccades (Fig. 4*A*). The mean ± SD difference across all OPNs was −3.5 ± 8.5 ms. This measure was significantly different from zero (2-tailed *t*-test; $P < 0.05$). Thus relative to control trials, OPN pause onset was slightly earlier for resumed saccades.

The parameters of pause end with respect to saccade end were considered for four cases: single saccades of control trials (Fig. 5*A*), initial and resumed components (Fig. 5, *B* and *C*) of stimulation trials, and truncated saccades (Fig. 5*D*) of stimulation trials. For initial and resumed saccades, the range of the number of saccades averaged for each cell is the same as that stated for the pause onset analysis. Our stimulation parameters typically did not generate too many truncated saccades and, therefore our sample was rather low (range 1–12; mean 2).

Similar to the observations made for pause onset, the resumption of activity typically preceded the end of the saccade. The mean value of pause end with respect to saccade end, averaged over 28 OPNs, was −9.6 ± 5.2 ms for control saccades, and −6.5 ± 4.8 ms and −10.4 ± 5.44 ms for the initial and resumed components, respectively. The analogous measure for truncated saccades, averaged >16 OPNs, was −6.8 ± 9.8 ms for truncated movements, where the large variability likely reflects the scarce data.

Next we compute the difference in time for the resumption of discharge at the end of initial, resumed, and truncated movements compared with the resumption time at the end of control saccades. The distribution of these differences (stimulation trial − control trial) of all OPNs is plotted in Fig. 6 for the three types of perturbed saccades. In interpreting these data, it is helpful to remember the convention that all discharge resumption time is negative if it leads saccade end. Thus a positive difference means that the discharge for control saccades was, on average, earlier (with respect to saccade end) in comparison with the resumption for a perturbed movement. For the initial component (Fig. 6*A*), the average difference was 3.1 ± 4.3 ms, which was significantly different from zero (2-tailed *t*-test, $P < 0.001$). Eight of the 28 OPNs had a mean difference significantly greater than zero (1-tailed *t*-test, $P < 0.05$). The mean difference in the time of resumption of activity before the end of the resumed saccade (Fig. 6*B*) was −0.8 ± 3.3 ms, and this difference was *not* significantly different from zero (2-tailed *t*-test, $P > 0.2$). Only 2 of the 28 OPNs exhibited a mean difference significantly greater than zero (1-tailed *t*-test, $P < 0.05$) for this condition. For truncated saccades (Fig. 6*C*), the mean deviation for our sample of OPNs

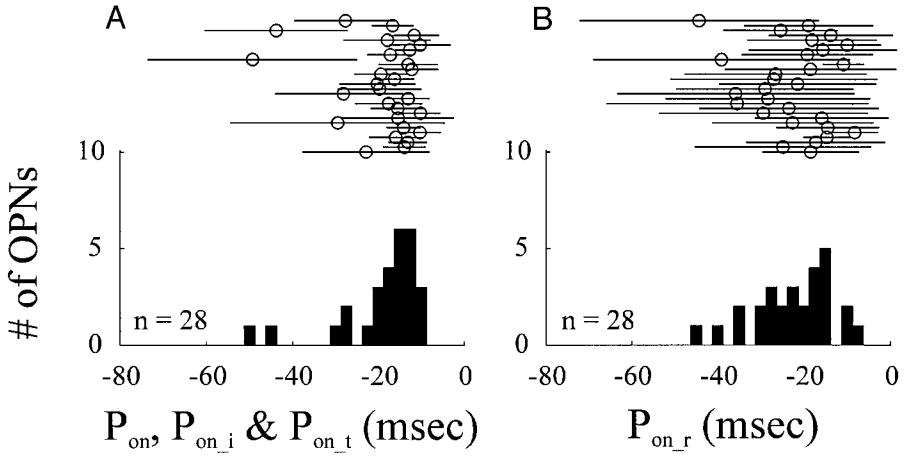

FIG. 4. Timing of pause onset with respect to saccade onset. Because saccade onset occurred before stimulation onset, the pause onset response of OPNs is the same for control and stimulation trials. *A*: subplot shows the distribution of pause onset with respect to saccade onset (P_{on}, P_{on_i}, and P_{on_t}), averaged over all trials for each OPN. ○, mean pause onset value for each OPN; —, ±1 SD. *B*: distribution of the same analysis for pause onset with respect to the onset of resumed saccades (P_{on_r}) of stimulation trials. Number at the *bottom-left region* of each subplot indicates the number of OPNs analyzed.

was 3.6 ± 8.7 ms, but this measure was not significantly different from zero (2-tailed *t*-test, $P > 0.1$). Only 1 of the 16 OPNs fulfilling this condition had a mean difference significantly greater than zero (1-tailed *t*-test, $P < 0.05$). Perhaps with a bigger data set, the mean pause end measure for truncated saccades might have been significant as well. Overall the mean shift for initial and truncated saccades are similar and positive.

Time of resumption of OPN activity: dependence on SC stimulation site

It is clear from our experiments that the OPNs resume discharge during the period between the end of the initial component and the onset of the resumed saccade (Fig. 2). When does the resumption occur with respect to stimulation onset? Is the timing of the resumption dependent on the stimulation site in the SC? The time from the stimulation onset to the resumption of activity (P_{end_stim}) was determined for each stimulation trial (see Fig. 3*B*). The mean value for each OPN as a function of stimulation site was pooled across all saccades in all directions and is plotted in Fig. 7. The *x* axis denotes the locations of the stimulation sites along the rostralcaudal axis of the SC, and the *y* axis indicates the time from stimulation onset to the resumption of OPN discharge. Note that several OPNs sometimes correspond to the same SC site. This is a consequence of recording more than one OPN on a given track while the stimulation site within the SC was fixed. Linear regression

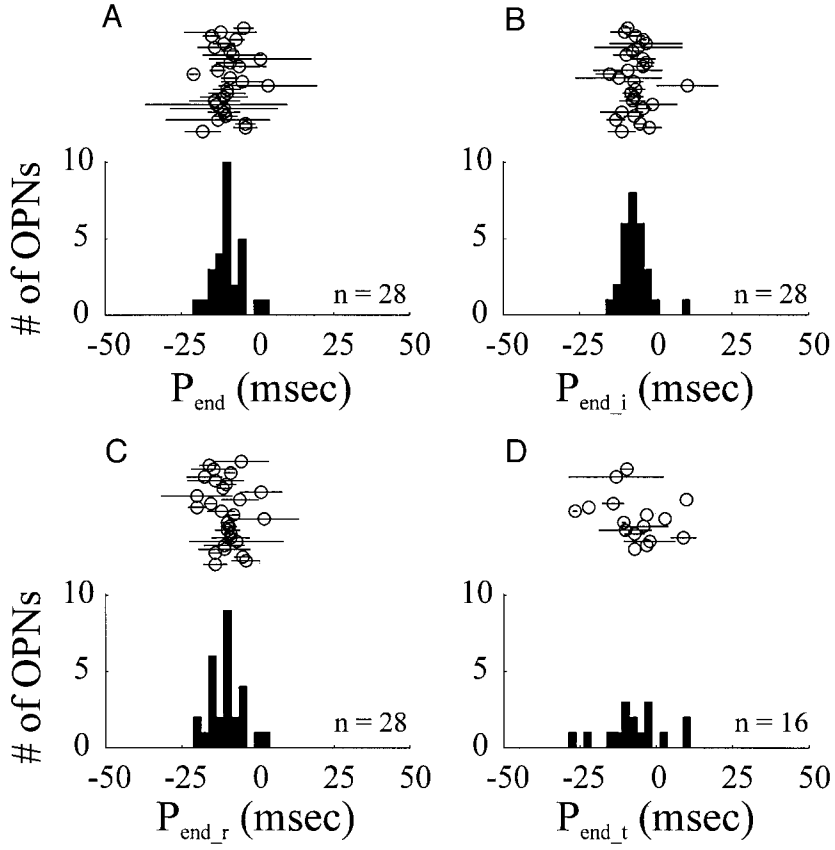

FIG. 5. Timing of pause end with respect to end of control saccades (P_{end}; *A*), initial components (P_{end_i}; *B*), resumed components (P_{end_r}; *C*), and truncated saccades (P_{end_t}; *D*). Format of figure is similar to Fig. 4. For several OPNs, only a single truncated saccade trial was recorded during stimulation of a specific SC site. Consequently, ○ representing these OPNs in *D* do not have a horizontal, standard deviation bar.

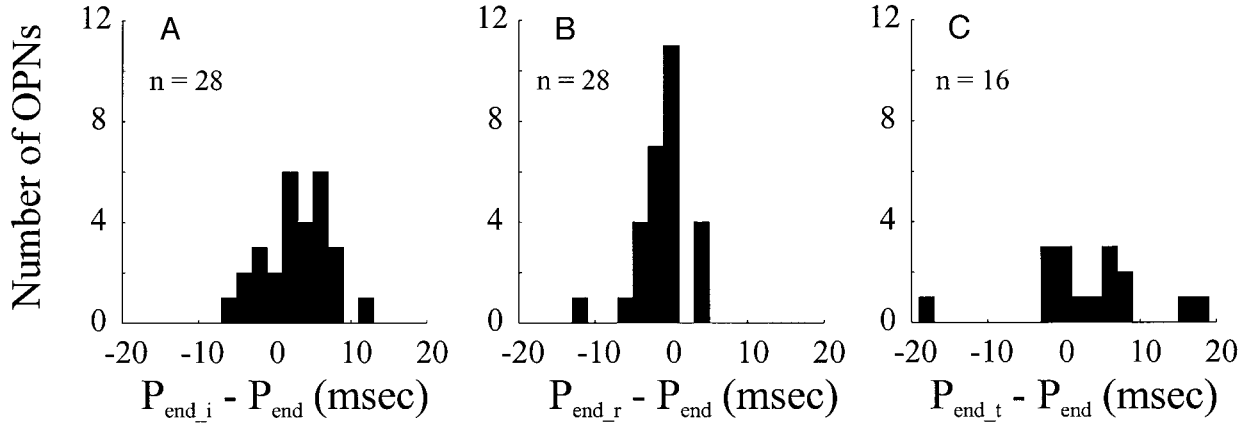

FIG. 6. Shifts in the time from pause end to saccade end for stimulation trials relative to control saccades. *A*: shift in OPN pause end for initial saccades (P_{end_i}–P_{end}). *B*: shift in OPN pause end for resumed saccades (P_{end_r}–P_{end}). *C*: shift in OPN pause end for truncated saccades (P_{end_t}–P_{end}).

through the data points yielded a slope that was not significantly different from zero (2-tailed *t*-test, $P > 0.05$).

Discharge rate properties

We next address the theory that the resumption of OPN activity instantaneously zeros the resettable neural integrator (Moschovakis 1994). To test this hypothesis, we measured the firing rate before saccade onset and after saccade end for control and all stimulation trials. We also recorded the activity during the interruption period (I_{dur} in Fig. 3*B*) for perturbed saccades with an initial and resumed component. The data then were available to determine whether the activity during the interruption period more closely matched the presaccade discharge, the postsaccade activity, both, or neither. The metrics computed to measured the activity for both control and stimulation trials are schematized in Fig. 3.

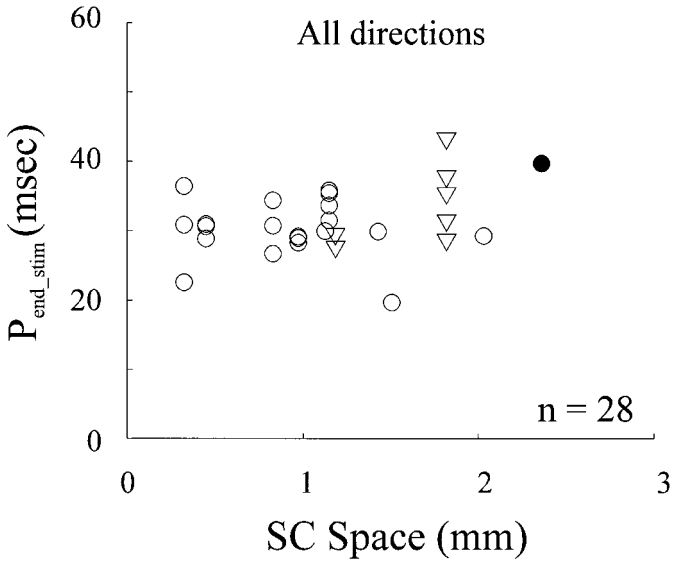

FIG. 7. Time from stimulation onset to resumption of activity in OPNs (P_{end_stim}) as a function of stimulation site in the SC. Abscissa, termed "SC Space (mm)," refers to the rostralcaudal component of the stimulation site, determined by converting the fixed vector saccade into collicular coordinates (Ottes et al. 1986). ○, *monkey BA;* △, *monkey HB.* ●, from *monkey BA,* represents the 1 OPN recorded when stimulation was applied just caudal to the 2 mm site. Because targeted saccades in the same direction as the fixed vector saccade (FVS) are accelerated (Gandhi and Keller 1999), only trials for which the target and FVS directions were orthogonal or opposite were averaged for this OPN. See text for more details.

To determine the presaccade activity, the number of spikes within a 50-ms window, ranging from 75 to 125 ms before saccade onset (shaded region before saccade onset), was counted for each trial. We chose not to measure over the 50-ms epoch immediately preceding saccade onset because the saccade-related suppression of OPNs may occur gradually, in a two-step process (Kamogawa et al. 1983; but see Everling et al. 1998). In our sample of OPNs, some showed a gradual decay that started well before saccade onset, whereas others showed a more step-like suppression just before saccade onset. The epoch over which we measured the presaccadic discharge was also not contaminated by a potential, transient target onset response (Everling et al. 1998) as these saccades were executed in the dark during a delayed saccade task.

The postsaccade measure was computed by counting the number of spikes within the 50-ms window after the end of the saccade (the shaded region after saccade end). For stimulation trials with initial and resumed components, the postsaccade measure refers to the end of the resumed saccade (Fig. 3*B*). The number of spikes for both measures was converted into average discharge rate (spikes per second) by dividing the number of spikes by 0.05 s. Note that all presaccade measures occurred before stimulation was delivered. These parameters theoretically have the same distribution for control and stimulation trials and, therefore were determined after combining all trials. The windows used to measure presaccade and postsaccade activity for truncated trials were the same as those considered for control saccades.

For the stimulation condition, the resumption of activity during the interruption period (I_{dur} in Fig. 3*B*) also was measured. For each trial, the number of spikes that occurred after pause onset of the initial saccade and before pause end associated with the resumed saccade was determined and divided by the interruption duration (I_{dur}). Trials in which no resumption activity occurred during the interruption period were discarded. The firing rates during the presaccade, postsaccade and interruption events then were averaged over the number of trials to yield a mean value for each OPN.

The relationship of the average activity before saccade onset

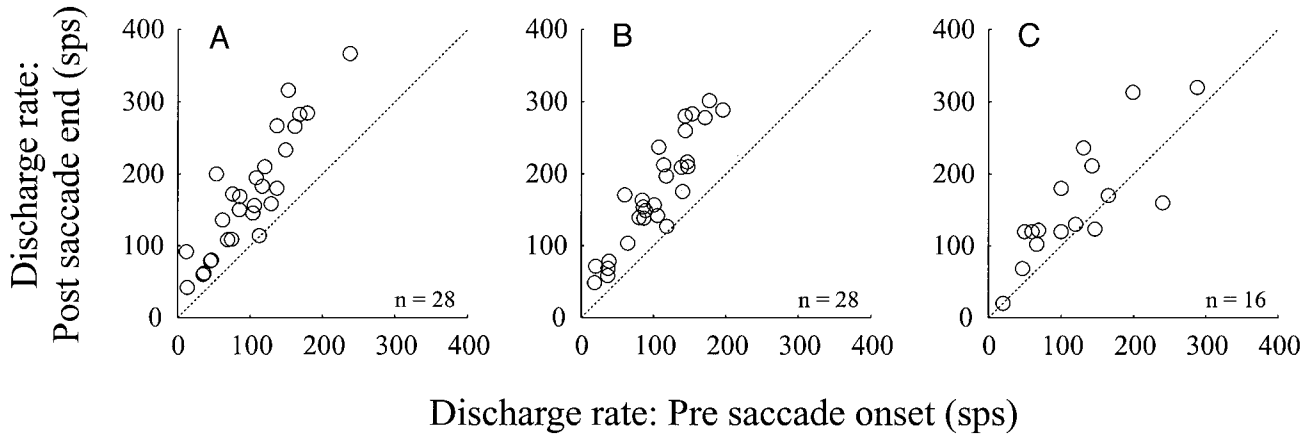

FIG. 8. Demonstration that omnipause neurons exhibit an enhanced postsaccade response. Postsaccade activity as a function of presaccade activity during control eye movements (*A*), resumed components of stimulated saccades (*B*), and truncated saccades (*C*). ○, OPN; *n* = indicates number of OPNs.

was plotted against the average activity after control saccade end (Fig. 8*A*), after resumed saccade end (Fig. 8*B*) and after truncated saccade end (Fig. 8*C*). Most of the OPNs in our sample displayed an enhanced postsaccadic discharge for all conditions, as shown previously (Everling et al. 1998). For each OPN, the average postsaccade activity was divided by its average presaccade rate, and a Student's *t*-test then was performed to determine whether the resulting distribution had a mean greater than one. The presaccade activity was significantly lower than the postsaccade rate for the control and stimulated saccades regardless of whether or not a resumed component was generated (1-tailed *t*-test, $P < 0.001$).

Similarly, the activity of the OPNs during the interruption period of stimulation trials (i.e., those with a resumed component) was compared with their presaccade (Fig. 9*A*) and postsaccade activity measures (Fig. 9*B*). As stated in the preceding text, statistical analyses were performed by normalizing the mean firing rate during the interruption by the average presaccade and postsaccade response and then determining whether the distribution had a mean greater than one. The level of activity during the interruption was significantly greater than the presaccade firing rate (1 tailed *t*-test, $P < 0.001$) but not significantly greater than the postsaccade discharge rate (1-tailed *t*-test, $P > 0.1$).

Because saccades truncated by the stimulation lacked a resumed eye movement, we sought to determine if the postsaccade activity on these trials more closely resembled the interruption duration activity or the postsaccade response observed during perturbed saccades with the second component. This issue was addressed by the analysis illustrated in Fig. 10. For the statistical analysis, we computed the ratio of the postsaccade activity of truncated trials to the activity during the interruption period and to the postsaccade activity after resumed movements. In both cases, the mean ratio of the distribution was *not* significantly greater than one (1-tailed *t*-test, $P > 0.1$).

DISCUSSION

Omnipause neurons in monkey discharge during fixation and suppress activity during saccades in all directions (Cohen and Henn 1972; Everling et al. 1998; Fuchs et al. 1991; Gandhi 1997; Keller 1974; Luschei and Fuchs 1972). Similar findings also have been reported in the head-fixed as well as head-free cat (Evinger et al. 1982; Paré and Guitton 1990, 1994b,c, 1998; Petit et al. 1999) and head-free monkey (Phillips et al. 1999). Our contribution to this literature is that when ongoing saccades are stopped temporarily in midflight by stimulation of the SC, the activity in OPNs resumes for the duration of the interruption period. In general, the pause onset occurred before saccade onset and pause cessation preceded the saccade end (defined by a velocity threshold criterion). When measured

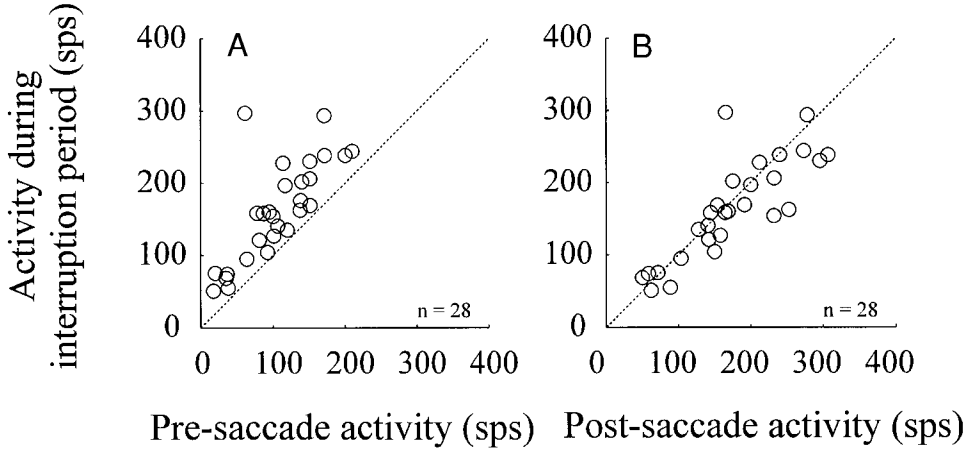

FIG. 9. Resumption of activity in OPNs during the interruption period (stimulation trials only). Activity during the interruption period is plotted as function of presaccade activity (*A*) and postresumed saccade discharge rate (*B*). Same format as Fig. 8.

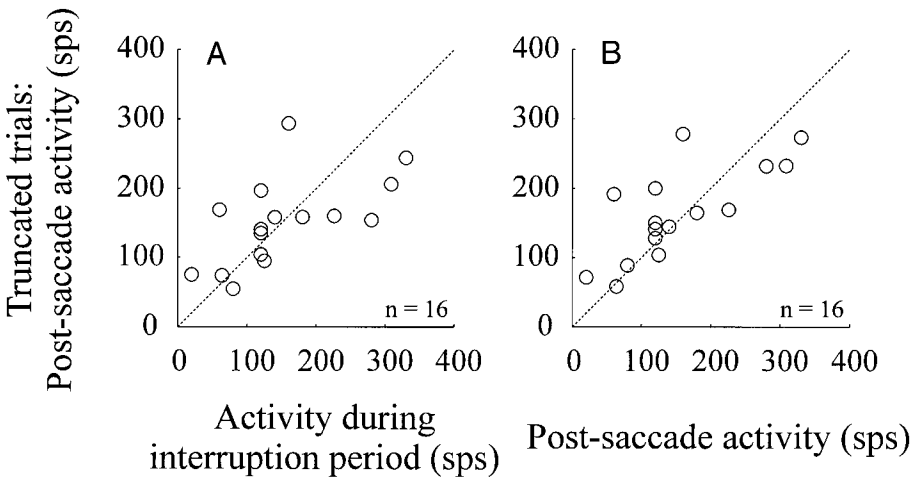

FIG. 10. Comparison of OPN discharge rate of truncated saccades with stimulation trials that produced a resumed component. Discharge rate after truncated saccade is plotted as function of the activity during the interruption period (*A*) and the discharge rate after the resumed saccade (*B*). Same format as Fig. 8.

with respect to saccade end, the OPNs resumed activity on average ~3 ms later for the initial component of stimulation trials than for either control or resumed movements. In addition, the OPNs typically exhibit a postsaccade enhancement (Everling et al. 1998), and this enhancement also is seen in the discharge during the interruption period.

Functional importance of superior colliculus projections to the omnipause neurons

Experiments that recorded neural activity as well as stimulated and lesioned the fixation neurons in the rostral pole of the SC (e.g., Munoz and Wurtz 1993a,b) have suggested that this region, which has been termed the fixation zone, is functionally different from the saccade zone in remainder of the SC (Munoz and Istvan 1998; Munoz and Wurtz 1995b; Munoz et al. 1993). Specifically, by making excitatory projections onto the OPNs in the brain stem, collicular fixation neurons are hypothesized to participate in solidifying visual fixation and preventing saccade generation (Munoz and Guitton 1989, 1991; Munoz and Wurtz 1993a). When the fixation zone is stimulated at the onset of large saccades, the ongoing eye movement is temporarily stopped in midflight presumably because the microstimulation reactivates the OPNs, which in turn stop the eye movement (Munoz and Wurtz 1993b). Then what predictions can be made regarding the timing of resumption of activity in the OPNs?

Microstimulation of the SC *during fixation* orthodromically activates the OPNs at monosynaptic and disynaptic latencies (King et al. 1980; Paré and Guitton 1994a; Raybourn and Keller 1977). Thus it is conceivable that microstimulation *during saccades* would activate the OPNs at similar latencies. The data plotted in Fig. 7 show that most OPNs were activated at latencies >20 ms after stimulation onset, well beyond the short-latency range expected on the basis of direct, excitatory connections. We suspect that during saccades the EBNs in the PPRF burst vigorously and indirectly inhibit the OPNs via the latch mechanism (Moschovakis et al. 1996; Robinson 1975) and that the excitatory input to the OPNs due to the microstimulation of the SC may not be sufficient to immediately overcome the inhibition. During fixation, the EBNs are not active and therefore cannot activate the latch pathway to inhibit the OPNs, which are directly activated by stimulation of the SC. Analogously, although the EBNs are not activated by stimulation of the primate SC during fixation (Raybourn and Keller 1977) presumably because of the inhibition exerted by the OPNs, monosynaptic latency activation has been demonstrated during saccades in the cat (Chimoto et al. 1996).

Consequently, the resumption of OPN discharge occurs as the effects of the microstimulation is processed by the neural circuits that control saccades (see following text). The excitation of the direct pathway from the SC to the OPNs is not sufficient to reactivate the latter neurons during saccades. Even the reactivation time with respect to stimulation onset ($P_{\text{end\_stim}}$), when plotted as a function of stimulation site (Fig. 7), does not produce a statistically significant trend, despite the spatial distribution of SC projections to the OPNs (Büttner-Ennever and Horn 1994; Gandhi and Keller 1997a; Paré and Guitton 1994a).

Independent of the mechanism by which the OPNs resume activity, the end of the pause relative to the end of the saccade should be similar for control trials, truncated movements and the initial and resumed components of perturbed saccades. In addition, because the instantaneous discharge frequency of EBNs is greater during a saccade then near the end of the movement (Van Gisbergen et al. 1981), a stronger inhibition by the OPNs may be required to suppress the ongoing EBN discharge to stop the movement. Therefore we also considered the possibility that the mean lead time of resumption of OPN activity with respect to the end of the initial component could be greater than the equivalent measure for control and resumed saccades. Our experimental data, plotted in Fig. 6, instead show that the lead time of activity resumption with respect to initial saccade end was *shorter* than for control or resumed movements, an observation significantly in contrast to that expected. In sum, despite the extensive excitatory projections from the rostral SC to the OPN region, fixation neurons do not have sole control over OPN response and therefore are more likely play a supportive role in saccade control. Similar interpretations also have been made based on a quantitative comparison of the resting discharge rates and the timing of pauses of these two types of neurons (Everling et al. 1998).

Then what additional mechanisms could explain the timing of the OPN response during saccades perturbed by SC stimulation? We elaborate on a scheme, briefly mentioned by Munoz and Wurtz (1993a), that exploits intracollicular interactions (Arai et al. 1994; Behan and Kime 1996; Lee et al. 1997;

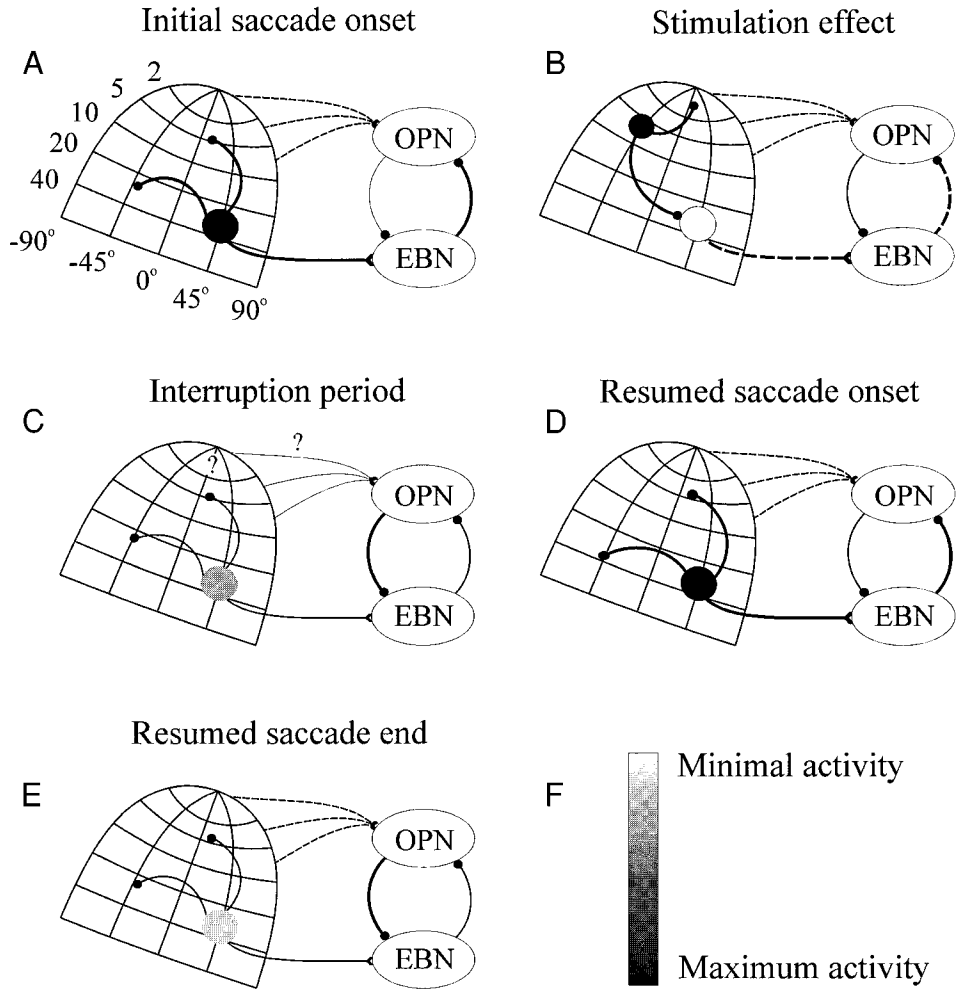

FIG. 11. A conceptual model of the interactions within the SC and between the SC and OPNs and excitatory burst neurons (EBNs) to explain the temporal sequence of activation of OPNs observed during saccades perturbed by SC stimulation. See text for details. SC schematic is based on the model of Ottes et al. (1986), where the iso-amplitude meridians run medial-lateral and iso-direction lines go rostral-caudal. Projection from SC to EBNs, although spatially distributed (Moschovakis et al. 1998), is lumped into 1 projection for simplicity and is considered to have crossed the midline. However, the spatial distribution of SC projections to the OPNs is shown by 3 curves to dispel the notion of a discrete fixation zone. Shade of the circles at different loci on the SC map refers to the level of activity, based on the grayscale shown in (F). Inhibitory projection from the EBNs to the OPNs is believed to be mediated by inhibitory latch neurons. Thickness of each line suggests the activity in the projection–the bolder the solid line, the more active the connection. Dashed lines represent disfacilitation. Projections ending with a filled circle are inhibitory, whereas those ending with "<" are excitatory.

Meredith and Ramoa 1998; Munoz and Istvan 1998; Pettit et al. 1999) to disinhibit the OPNs by a rapid disfacilitation of the EBNs (Fig. 11). The conceptual model sketches the effective connections during five temporal epochs of a saccade trial. Each subplot shows a schematic of the saccadic motor map (Ottes et al. 1986; Robinson 1972), the OPN region and the contralateral EBNs. The spatial distribution of the SC projections to the OPNs is represented by three curves to dispel the notion of a discrete fixation zone. The SC projections to the EBNs, although also spatially distributed (Moschovakis et al. 1998), is lumped into one projections for clarity in the diagram. Local excitation within the SC (Arai et al. 1994; Lee et al. 1997; Pettit et al. 1999) is indicated by a circle to represent an active population of neurons, and distant inhibition (Meredith and Ramoa 1998; Munoz and Istvan 1998) is shown by projections between far regions of the SC.

At the onset of a saccade the target activated population of SC neurons, which discharge maximally, is shown as dark circles (Fig. 11*A*). The inhibitory influence of the active population onto distant SC sites is represented by two thick inhibitory projections. Note that the inhibition is global to distant saccade zone regions not just the rostral fixation zone site (Meredith and Ramoa 1998; Munoz and Istvan 1998). The suppression of activity in collicular neurons that excite the OPNs disfacilitate the latter neurons; thus these projections are drawn as a dashed line (Fig. 11*A*). Furthermore the active burst neurons within the SC directly and indirectly excite the EBNs (Chimoto et al. 1996; Raybourn and Keller 1977). When active, the EBNs inhibit the OPNs indirectly via the latch pathway (Moschovakis et al. 1996; Robinson 1975). The EBNs deliver a velocity command that innervates the extraocular muscles and initiates a saccade.

Microstimulation of a SC site is triggered on the onset of saccades (Fig. 11*B*, open circle). Inhibitory intracollicular connections (Meredith and Ramoa 1998; Munoz and Istvan 1998) almost immediately suppress activity in distant regions, including the already silent rostral pole (which maintains the disfacilitation of OPNs) and the target activated caudal site (now shown as open circle). Indeed, Munoz et al. (1996) stimulated the fixation zone to perturb ongoing saccades and observed that the response at the site activated before the large saccade is turned off, at least momentarily. Analogous discharge profiles of SC neurons also have been recorded when the stimulation was applied to extracollicular structures such as the OPN region (Keller and Edelman 1994; Keller et al. 1999) and the frontal eye fields (Schlag-Rey et al. 1992). We propose that the rapid decrease in activity of burst neurons in the caudal SC instantaneously removes the vigorous input to the EBNs, withdrawing the command to drive the eyes and, furthermore, disinhibiting the OPNs (thick *dashed* projections).

The interruption period commences next (Fig. 11*C*). The OPNs discharge at a constant rate during this epoch and, thus

inhibit the EBNs. Some SC neurons exhibit a low-frequency discharge after a transient suppression (rostral SC stimulation: Munoz et al. 1996; OPN stimulation: Keller et al. 1999), as if in preparation for the next movement (gray circle at the target activated site in the SC). Because SC neurons are not discharging maximally during the interruption period, their activity is represented as a gray circle and their inhibition on distant sites is shown by thin solid curves.

It is not clear, on the other hand, how neurons in the rostral pole of SC respond during the interruption period. Therefore a question mark is used to denote this lack of knowledge (Fig. 11*C*). Several preliminary studies have shown that some rostral SC neurons do not resume discharge, whereas others are activated but with rather sporadic firing rates (Bergeron and Guitton 1997; Gandhi and Keller 1996; Munoz et al. 1996). Our current experiments have shown that the SC inputs to the OPNs are not solely responsible for the resumption of spike discharge in the latter neurons. Therefore we show these projections as thin solid lines to indicate their lessor importance with respect to the increasing excitatory drive to EBNs from caudal SC neurons (Fig. 11*C*, gray circle).

Next, the resumed saccade is generated (Fig. 11*D*). The active circuitry is much like that proposed for initial saccade onset (Fig. 11*A*), except that the pause onset time is more variable (Fig. 4*B*). This variability may be due to the fact that the ensemble discharge at the caudal SC site resumes discharge with more variability and never achieves the level of activity that it displays at initial saccade onset (Keller and Edelman 1994).

Toward the end of the resumed saccade (Fig. 11*E*), neural activity in burst neurons in the caudal SC decreases to $<10\%$ of the peak activity (Anderson et al. 1998; Munoz and Wurtz 1995a; Waitzman et al. 1991)—modeled as a light gray circle—and hence reduces its inhibition onto distant regions of the SC—drawn as thin, solid curves. As motor error reaches zero, so does the discharge rate of EBNs (Van Gisbergen et al. 1981) and most SC neurons. When the inhibitory effect of EBNs onto OPNs drops below a threshold, the OPNs are disinhibited (Gandhi and Keller 1997a; Kaneko 1996). The latter group of neurons then comes back on, gates the saccadic burst generator (thick inhibitory projection from the OPNs to the EBNs) and assists in ending the saccade. Note that OPN resumption leads rostral SC neurons reactivation (Everling et al. 1998). Thus activity is not represented in the rostral SC during this temporal epoch.

It is necessary to emphasize the subtle difference in the reactivation of OPNs at the end of the initial and control saccades. In the former case, stimulation of the SC *rapidly* removes the input from the EBNs, whereas in the latter situation the decline of discharge in both SC burst neurons and EBNs is relatively gradual. Although, in both cases, the OPNs resume discharge when the inhibitory influence from the EBNs drops below a threshold, a velocity command approaches zero faster for the initial component, making the end of the initial saccade less (or not) dependent on the resumption of the OPNs.

The series of events outlined in the preceding text is only intended to clarify possible interactions between the SC and the saccadic burst generator. For example, the caudal fastigial nucleus in the cerebellum, although not represented in the schematic, also contributes to the balance of activity between EBNs and OPNs and the rostral and caudal SC (Goffart and Pélisson 1998; Lefèvre et al. 1998; May et al. 1990; Sato and Noda 1991).

Resettable neural integrator

We tested the hypothesis that the OPNs zero the resettable neural integrator. We used the approach of recording neural activity of OPNs during saccades and searching for differences in pre- and postsaccade discharge properties. The discharge rate of the population of OPNs before saccade onset was found to be significantly lower than the activity immediately after saccade end (Fig. 8). Furthermore the discharge rate during the interruption period of saccades perturbed by SC stimulation was similar to the postsaccade firing frequency (Fig. 9). An examination of the OPN response during truncated saccades (Fig. 10) also produced similar results. Hence from the perspective of the OPNs, the end of an initial component of a perturbed saccade is equivalent to the end of a control eye movement. In other words, if the OPNs zero the resettable integrator at the end of a saccade, then they also do so at the end of the initial saccade.

Several experiments have provided results that allow an examination of the resettable neural integrator hypotheses. Keller and Edelman (1994) recorded from collicular neurons during interrupted saccades induced by OPN stimulation and tested for spatial transformation of activity on the SC map. Typically premotor activity at a particular locus in the deeper layers of the SC produces a saccade coded by that site. Because interrupted saccades have initial and resumed components, the locus of activity in the SC for the resumed saccades should be mapped to a more rostral site if the resettable neural integrator is reset and the saccadic system considers the two components as independent saccades. Instead the same SC site active for the initial component of the saccade was reactivated for the resumed component (Keller and Edelman 1994). Munoz et al. (1996) reported the same finding during saccades perturbed by stimulation of the rostral pole of the SC.

One may argue, however, that the decay of the resettable neural integrator follows an exponential process (Kustov and Robinson 1995; Nichols and Sparks 1995) and that the spatial remapping in the SC is observed only after the resettable neural integrator has completely discharged to zero. If so, the amplitude of the resumed saccade becomes dependent on the initial saccade magnitude, the interruption duration, and the time constant of the decay. The observed amplitudes did not match the predicted outcomes, suggesting that the resettable neural integrator does not begin to decay exponentially at the end of the initial saccade (Keller et al. 1996). In addition, the metrics of sequential saccades to double-step stimuli (Goossens and Van Opstal 1997) and corrective saccades (Brown et al. 1997) also cast doubt on idea of a gradual decay in the resettable neural integrator.

This series of arguments suggests that the OPNs cannot signal the end of saccades and cannot solely zero the resettable neural integrator. Alternatively, the notion of the resettable neural integrator may be incorrect. The signals processed by the internal feedback pathway may accurately reflect eye position irrespective of preceding movements (Dassonville et al. 1992; Goossens and Van Opstal 1997; Keller et al. 1996; Schlag et al. 1998).

Enhanced postsaccade response

The postsaccade enhanced response in the OPNs in monkey has been observed previously (see Fig. 6*C*) (Everling et al. 1998; Gandhi 1997; Luschei and Fuchs 1972). In contrast, cat OPNs do not exhibit an enhanced response and some even buildup slowly to the presaccade rate (Paré and Guitton 1994c). The increase in OPN discharge rate observed in monkey might result from either postinhibitory rebound and/or increased excitatory input.

Receptors on dendrites of OPNs are immunoreactive for glutamate (Horn et al. 1994). Thus excitatory inputs likely contribute to the production of the postsaccade enhanced response. They also may maintain the constant activity observed during fixation since the discharge rate slows and often stops completely during a state of reduced alertness (Henn et al. 1984; Raybourn and Keller 1977). Although the origins of excitatory input to OPNs have not been demonstrated unequivocally, probable sources are from neurons that also tend to exhibit tonic discharge. Monosynaptic connections from the deeper layers of the SC (Paré and Guitton 1994a; Raybourn and Keller 1977) and from the eighth cranial nerve (Keller 1977) have been orthodromically confirmed. In addition, anatomic studies have identified OPN afferents to originate from various nuclei of the vestibular system, the fastigial nucleus of the cerebellum and other brainstem areas (Ito et al. 1984; Langer and Kaneko 1984, 1990).

Of all these projections to the OPNs, the physiology of the SC inputs is perhaps best understood. However, on the basis of their timing of pause onset and end, excitatory SC inputs can at best modulate the activity of OPNs and not produce either the sharp inhibition at saccade onset or the enhanced reactivation at saccade end (Everling et al. 1998; Gandhi 1997). Hence the postsaccade enhanced response may result from yet undiscovered excitatory inputs or from a biophysical membrane property called postinhibitory rebound. Postinhibitory rebound is a transient depolarization after a hyperpolarization, where the magnitude of the response depends on the parameters of the hyperpolarization (Bertrand and Cazalets 1998; Dean et al. 1989; Roberts and Tunstall 1990). Although postinhibitory rebound has not been specifically tested in the OPNs, the somata of OPNs have ample receptors for glycine (Horn et al. 1994). Postinhibitory rebound has been observed in glycinergic spinal cord neurons involved in, for instance, locomotion (Bertrand and Cazalets 1998; Soffe 1991). In addition, Enderle and Engelken (1995) have postulated that postinhibitory rebound responses in neurons in the PPRF account for the variability in saccade dynamics.

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Present address of N. J. Gandhi: Division of Neuroscience, S-515, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Address for reprint requests: E. L. Keller, The Smith-Kettlewell Eye Research Institute, 2318 Fillmore Street, San Francisco, CA 94115.

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