Discharge Characteristics of Vestibular Saccade Neurons in Alert Monkeys

CHRIS R. S. KANEKO AND KIKURO FUKUSHIMA
Department of Physiology and Biophysics and Regional Primate Research Center, University of Washington, Seattle, Washington 98195; and Department of Physiology, Hokkaido University School of Medicine, Sapporo 060, Japan

Kaneko, Chris R. S. and Kikuro Fukushima. Discharge characteristics of vestibular saccade neurons in alert monkeys. J. Neurophysiol. 79: 835–847, 1998. We previously described a class of neurons, located in and around the interstitial nucleus of Cajal of the cat, that discharged during vestibular stimulation and before saccades. We called these neurons vestibular saccade neurons (VSNs). In the present study, we characterized similar neurons in the monkey. These neurons discharged before vertical saccades and during vertical vestibular stimulation as well as vertical smooth pursuit. Like cat VSNs, the discharge metrics of these VSNs were poorly related to saccade metrics and showed only occasional, weak sensitivity to eye position. They discharged most intensely (on-direction) for movements that were either upward or downward, and their on-directions were consistent during pitch and pursuit but not for eye position. For saccades, the correlation coefficient of number of spikes and vertical saccade size varied from 0.08 to 0.90 with a mean of ~0.6. The average sensitivity (i.e., slope) of the number of spikes and vertical saccade size linear regression was 0.3 ± 0.2 spike/deg. Average correlations between peak discharge rate and peak saccade velocity and between burst duration and saccade duration were 0.5 and 0.4; sensitivities were 0.2 ± 0.2 spike/s per deg/s and 0.6 ± 0.5 ms/ms, respectively. Average vestibular sensitivities during 0.5 Hz, ±10° sinusoidal pitch while the animals suppressed their vestibular ocular reflex were 0.97 spike/s per deg/s for up VSNs and 0.66 spike/s per deg/s for down VSNs. The average static position sensitivity for the population of 39 VSNs tested was 0.55 spike/s per deg. The average gain for VSNs tested during 0.5 Hz, ±10° sinusoidal smooth pursuit tracking was 1.4 spike/s per deg/s. As we could not identify analogous neurons in the region of the monkey pontomedullary junction, we conclude that horizontal on-direction VSNs do not exist in the monkey. We discuss a possible functional role for VSNs and similar neurons described in previous studies and conclude that these neurons are most likely involved with the process of neural integration (in a mathematical sense) of velocity-coded inputs from a variety of oculomotor subsystems and are not a pivotal element in saccade generation.

INTRODUCTION

The saccadic eye movement system is one of the best understood motor systems in mammals (for comprehensive reviews, see Wurtz and Goldberg 1989). Saccades are created by a burst generator whose neurons lie in reticular structures, so it has been difficult to identify their inputs. One major input arises from the superior colliculus; however, the colliculus is not essential for production of saccades (Albano and Wurtz 1982), so other sources of input also must be able to activate the saccade generator. Another possible direct input to the burst generator in cats may be contributed by neurons called burster driving neurons (BDNs) (Kitama et al. 1992a, b, 1995; Ohki et al. 1988). These neurons project to the contralateral pontine burst generator, discharge for saccades, have a type II vestibular response (Duensing and Schaefer 1958; Shimazu and Precht 1965), and are activated at disynaptic latencies after electrical stimulation of the contralateral vestibular nerve (Ohki et al. 1988). In addition, they have discharge metrics that are correlated with the metrics of horizontal saccades, they receive di- or trisynaptic input from the superior colliculus, and they respond to contralaterally moving visual stimuli (Kitama et al. 1992a, b, 1995). Kitama et al. (1995) have suggested that the colliculo-BDN-burst generator pathway is one of several parallel pathways whereby saccade signals are relayed to the pontine burst generator. The function of this pathway is modulated by vestibular input and may promote ipsilateral saccades during head rotation (Kitama et al. 1992a, b, 1995).

We recently described what we called vestibular and saccadic neurons (VSNs) in the interstitial nucleus of Cajal (INC) in cats (Fukushima et al. 1995). VSNs discharged during pitch rotation as well as before vertical saccadic eye movements, and about half showed some eye position sensitivity. Maximum activation analysis (MAD) (Baker et al. 1984) suggested that the vestibular input was largely from the contralateral labyrinth; therefore, the neurons are type II just like BDNs except that they respond to vertical rather than to horizontal stimuli. The metrics of VSN discharge was correlated with the metrics of the vertical saccades, albeit less highly correlated than BDNs are with horizontal saccades, and 15 of 15 VSNs tested were activated after electrical stimulation of the contralateral vestibular nerve. Because their discharge is qualitatively similar to that of BDNs, we argued that VSNs might actually be vertical BDNs. However, as we pointed out, the lack of strong parametric correlations between discharge and saccade metrics and the existence of VSNs intermingled among the putative integrator neurons of the INC suggested an alternative interpretation: the discharge of VSNs may instead reflect the fact that they participate in the integration process. For example, VSNs could act as an input layer to the vertical neural integrator (see Fukushima et al. 1995 for discussion). In addition, the prominent vestibular sensitivity and the direct vestibular input of both VSNs and BDNs seems superfluous for a primarily saccadic function. The location of VSNs in the INC is also somewhat inconsistent because the INC usually is thought of as the neural integrator for vertical and torsional eye movements (for review, see Fukushima and Kaneko 1995; Fukushima et al. 1992).
In this study, we had three objectives in investigating possible VSNs in the monkey. First, we sought to confirm their existence in primates and then take advantage of the richer simian behavioral repertoire to obtain further details about their discharge sensitivities. Second, we wanted to examine VSNs as a possible new and important source of input to the saccade generator. Finally, we wanted to see if we could distinguish between the alternative hypotheses that had been suggested in our previous investigation of vertical VSNs in cats. In particular, we wanted to determine whether vertical VSNs are actually vertical BDNs and thus serve a saccade function or, alternatively, whether they are associated with the neural integrator in the INC and relay a variety of oculomotor inputs. A preliminary account of some of these findings has been published in abstract form (Kaneko and Fukushima 1993).

METHODS

Our methods were described elsewhere (Fukushima et al. 1995; Kaneko 1996, 1997) and are summarized briefly except where they differ. All experiments were performed in strict compliance with the Guide for the Care and Use of Laboratory Animals (Department of Health Education and Welfare Publication No. NIH85–23 1985) and recommendations from the Institute of Laboratory Animal Resources and the American Association for Accreditation of Laboratory Animal Care International. Specific protocols were approved by the Institutional Animal Care and Use Committee at the University of Washington (ACC No. 2602–01).

Four juvenile, male rhesus macaques (Macaca mulatta) were trained to track a laser spot for food reward during a variety of visual and vestibular stimulus situations. After the animals were prepared surgically and were trained in the tracking task, we explored two regions using standard extracellular electrophysiologically recording techniques. In the mesencephalon of monkeys C and W, we surveyed the INC and the neighboring reticular formation over the region corresponding to the rostro-caudal extent of the oculomotor nucleus and from the dorsum of the mesencephalon to the depth of the oculomotor nucleus. In the rostral medulla of monkeys M and Z, we canvassed the area from the caudal pole of the abducens nucleus caudally 4.5 mm and ±3.5 mm on each side of the midline and from the surface of the brain stem usually to a depth of 3–5 mm but never <2.5 mm.

We used a combination of behaviors as our search stimulus. The animals were trained to smoothly pursue a ∼0.5° red target spot moving at 0.5 Hz ± 10° either obliquely (pontine recordings) or vertically (mesencephalic recordings) while being rotated in the horizontal (0.4 Hz, ±10°) or vertical (0.25 Hz, ±10°) plane, respectively. As this is not an easy task, the animals required many retargeting saccades to stay close to the target. Thus we easily identified vestibular, smooth pursuit, and saccade-related discharge using this combined search stimulus. When a responsive neuron was encountered, it was tested in the following manner. For saccades, the target stepped randomly between points on a centered 7 × 5 array spaced at 5° intervals. Vestibular stimulation was accomplished by fixing the animal’s head rigidly to the primate chair and rotating the entire apparatus at ±10° and a variety of frequencies. To distinguish discharge related to the eye movements evoked by the vestibulo-ocular reflex (VOR) from that related to the vestibular input, we trained the monkeys to suppress their VOR by requiring them to fixate a target that moved with them so that the eyes did not move relative to the head. For smooth pursuit, we used sinusoidal, ±10° target movement at different frequencies; in monkey C, we also tested vertical ramp stimuli (10, 20, or 30°/s). To assess position sensitivity, we required the animal to fixate the target at various target eccentricities along the vertical or horizontal meridian.

Eye movements were digitized off-line from tape recordings of the data and analyzed with home-made interactive programs. Saccade analysis is described elsewhere (Fukushima et al. 1995; Kaneko 1996, 1997). Briefly, our program identified the saccades on the basis of adjustable velocity criteria, marked the target and saccade onset, offset, and peak velocity, and then calculated all the descriptive characteristics of the saccades. Each saccade was inspected and accepted, remarked, or rejected. For smooth pursuit, if the stimulus consisted of sinusoidal target movement, each cycle for a particular stimulus frequency was binned into 512 equal-duration bins and presented on a computer screen (the number of bins used in the analysis was unrelated to the number used for Figs. 5 and 7). The investigator marked any saccades or segments of poor tracking with a cursor, and those sections were deleted along with the associated neuronal discharge. The saccade duration was overestimated and the program automatically extended the deleted portion of the discharge to ensure that no saccade-related activity was included in the final histograms. The resulting segments and discharge were fit with a sinusoid by means of a least-squares method (Schor 1973). We tried to accumulate ≥10 cycles for each fit but occasionally settled for fewer owing to poor tracking by the animal or loss of isolation of the neuron recording. An individual cycle was not included in the final average if <60% of the data remained after editing or if the fit accounted for <80% of the variance. These criteria were needed only for the low frequencies of tracking during which saccades were proportionately more prevalent due to the binning process. The frequency histograms in Figs. 5 and 9 exclude the deleted discharge but the rasters are untouched. In monkey C, ramp stimuli also were used to produce smooth pursuit. For analysis of those data, each ramp was displayed on the computer screen and saccades again were marked manually for extirpation. Responses were averaged and presented along with rasters and histograms with the use of a second program that also allowed quantitative comparison of the pursuit and target movement metrics.

Vestibular-evoked eye movements were analyzed with the use of the cycle analysis program described above and thus differed slightly from the analysis in our cat study (Fukushima et al. 1995). Again, we usually collected ≥10 cycles unless the animals became drowsy during VOR in the dark or performed the suppression task poorly. The sinusoidal-fit variance criteria for rejection of a cycle were not applied to VOR data because the suppression and roll conditions (see VESTIBULAR EVOKED EYE MOVEMENTS IN RESULTS) resulted in minimal activation of the VOR and consequent low gains that yielded poor fits.

For vertical VSNs, we used MAD analysis (Baker et al. 1984) to distinguish which vertical canal provided the likely source of vestibular input. By rotating the animal in a number of different vertical planes positioned horizontally between the pitch and roll plane, we could reverse the relation between VSN discharge and direction of the rotation, thus indicating whether the VSNs received excitatory vestibular inputs mainly from the ipsilateral labyrinth, i.e., type I response, or the contralateral labyrinth, i.e., type II response (Duensing and Schaefer 1958; Fukushima et al. 1995; Shimazu and Precht 1965).

RESULTS

INC recordings

We recorded 55 neurons that responded to vestibular stimulation and discharged for vertical saccades in and around the INC of monkeys W and C. Because of their similarity to VSNs in the cat (Fukushima et al. 1995), these too will be called VSNs. Each of the VSNs was recorded during a vari-
ety of stimulus conditions, but not all conditions were applied to each VSN either because the recording isolation could not be maintained or because the animal stopped performing one or more of the various behavioral tasks that were required to assess the discharge sensitivities.

The location of one of the recorded VSNs from monkey W is shown in Fig. 1. Two marking lesions were placed on the track above (top arrow) and at the dorsal margin (bottom arrow) of the region where we recorded VSNs. The location of one such recording is indicated by the star just dorso-lateral to the oculomotor nucleus (OMC). Five VSNs were recorded on this track, and all the VSNs recorded from this side in monkey W were within 0.5 mm medial, 1.25 mm rostral, 0.75 mm caudal, and 1.0 mm lateral of this site. The dorso-ventral extent of the recordings is less certain due to the imprecision in aligning the depth of the microelectrode from track to track but all were recorded between 0.5 and 3.0 mm dorsal to the oculomotor nucleus. Reconstructions from the second chamber in monkey W and from monkey C revealed similar locations that are in and around the INC. Because VSNs occasionally were recorded laterally, where lateral margins of the INC are indistinct, some may have been outside the anatomically defined nucleus, as they were in cats (Fukushima et al. 1995).

SACCADIC. One defining characteristic of VSNs is their saccade-related discharge for vertical saccades. However, the metrics of the discharge in monkey VSNs are not usually well related to the metrics of the saccade, and it was often impossible to discern a consistent relation between VSN burst discharge and vertical saccades. For example, Fig. 2 shows the discharge of a typical VSN that usually fired in association with downward saccades (but note smaller bursts for upward saccades as well, middle 2 traces). This VSN also discharged for a 20° upward saccade (first arrow, second trace) as well as for a very small corrective saccade three bursts later (second arrow). In fact, many VSNs discharged bursts of action potentials that were not associated with any detectable eye movement but were as robust as bursts that accompanied saccades. In other instances, comparable saccades were associated with a burst on one occasion and a pause shortly thereafter. This lack of correlation was compounded by the fact that the saccade-related discharge varied from neuron to neuron so that it was quite robust in some neurons (e.g., Fig. 3) and barely noticeable in others. These findings are identical to those we previously documented for vertical VSNs recorded in and around the INC in cats (Fukushima et al. 1995). However, the variability in the discharge and the poor metrical relations are much more striking in the monkey because they contrast so sharply with the tight relations between saccade-related neurons that normally typify simians (see Fuchs et al. 1985; Moschovakis et al. 1996; Wurtz and Goldberg 1989).

Despite the large variability, VSNs show weak correlations, on average, between saccade and burst metrics. An example of a VSN that was well related to upward saccades is shown in Fig. 3. This was our most completely characterized unit, W 29:1. Scatter plots of the number of action potentials within the saccade-related burst (number of spikes) versus the amplitude of the vertical component of the saccade (vertical size) were fit with a least-squares linear regression that, in the example shown in Fig. 3A, yielded a correlation coefficient ($r$) of 0.87. Similar plots and fits are shown for the peak firing rate/peak vertical component velocity correlation (Fig. 3B) and for burst duration/vertical saccade duration (Fig. 3C).

For the population of VSNs ($n = 40$) with sufficient data, the correlation coefficients for the linear regressions between burst discharge metrics and saccade metrics ranged smoothly from 0 to 0.9 with no obvious grouping of the neurons at particular values (Fig. 4). The distribution did not seem to...
differ for up and down VSNs for any of the correlations (Fig. 4, A–C). For example, the correlation coefficient of number of spikes and vertical saccade size varied from 0.08 to 0.90 with a mean of −0.6 (Fig. 4A). Of the three correlations, the number of spikes and vertical saccade size showed the most clustering around a correlation of 0.6 to 0.7 (Fig. 4, compare A with B, C, and F). Peak firing rate/peak vertical component velocity averaged 0.5 and ranged from 0.03 to 0.89 (Fig. 4B), and the regression of burst duration/vertical saccade duration averaged 0.4 with a range of −0.29 to 0.73 (Fig. 4C) and a mean slope of 0.5 (range −1.15 to 1.10, Fig. 4F). Typically, there were a few VSNs that had particularly low correlations for one relation, but there was only one neuron that was poorly related to saccades in all of its metrics. The average sensitivity (i.e., slope) of the number of spikes and vertical saccade size linear regression was 0.3 ± 0.2 spike/deg and that of peak firing rate/peak vertical component velocity was 0.2 ± 0.2 spike/s per deg/s. On average, VSNs discharged for 0.6 ± 0.5 ms per millisecond of saccade duration (Fig. 4F). The average correlation coefficient for these metrics increased very little (0.02 for number of spikes and vertical saccade size; 0.08 for peak firing rate/peak vertical component velocity; 0.03 for burst duration/vertical saccade duration) when the range of sac-
VESTIBULAR SACCADE NEURONS IN ALERT MONKEYS 839

FIG. 4. Distribution of correlation coefficients for discharge and saccade metrics. Frequency histograms show the correlation coefficients for number of spikes and vertical saccade size (A), peak frequency and peak vertical velocity (B), burst duration and vertical saccade duration (C), lead time (D), on-direction (E), and the slope of the regression line as calculated in Fig. 3C for the correlations in C (F). □, up VSNs; □, down VSNs.

cades was restricted to nearly vertical (i.e., within ±30° of up or down; not shown). In general, the more vigorously the VSN discharged, the better its discharge was correlated with the movement metrics.

The on-direction of a neuron is defined as the polar direction for which the neuron discharges maximally. The slopes (i.e., positive vs. negative) of the number of spikes and vertical saccade size and the peak firing rate/peak vertical component velocity relations suggested that 12 VSNs preferred upward saccades and 28, downward. Although the correlations were often quite low and statistically nonsignificant, we could confirm suggested on-directions in most cases by plotting the number of action potentials in the burst against the direction of the saccade expressed as a polar angle (where right is 0°, up is 90°, etc.). An example is shown for W29:1 in Fig. 3D. The curved line is a third-order polynomial fit that approximates a sinusoidal function showing a peak of discharge for upward saccades. Even though the on-directions were consistent, as with the saccade metrics, the directionality of VSNs was sometimes only weak and varied from distinctly up or downward to nondirectional. Four of the 40 VSNs showed essentially no directional preference and another four showed weak preference (i.e., r < 0.3 for both number of spikes and vertical saccade size and peak firing rate/peak vertical component velocity), whereas only 10 were distinctly directional (i.e., r > 0.7 for either number of spikes and vertical saccade size or peak firing rate/peak vertical component velocity). The distribution of on-directions is plotted as a frequency histogram in Fig. 4E.

The lead time from the beginning of the burst to the beginning of the saccade also varied a great deal (Fig. 4D). Because the lead is longest in the on-direction of the neuron, we limited our measurements to on-direction saccades (i.e., within ±30° of the on-direction). Lead times ranged from nearly synchronous with saccade onset (0.8 ms) to 98 ms before the saccade with an average lead time of 32.5 ± 21 (SD) ms.

FIXATION. VSNs also have a modest eye position sensitivity, which was tested specifically in 12 VSNs and estimated from the discharge during intersaccadic intervals for another 27 neurons while the animal tracked the stepping spot in the saccade task. The relation between tonic firing rate and eye position varied considerably from trial to trial and neuron to neuron. This variability was reflected in the low correlation coefficients for the linear regressions relating these metrics. They ranged from 0.0 to 0.84 and were statistically significant for only half (19/39) of the VSNs tested (P < 0.01, t-test for significant regression). The average static position sensitivity (Kv) for the population of 39 VSNs tested was 0.55 spike/s per deg, which improved only slightly, to 0.87 spike/s per deg, if only the significantly correlated VSNs were considered. Finally, the on-direction of a VSN, as judged by its saccade sensitivity, was unrelated to the direction of increasing discharge during fixation. That is, VSNs could have upward on-directions and increase their tonic discharge for downward fixation positions and vice versa. About 60% had oppositely directed saccade and fixation on-directions.

VESTIBULAR EVOKED EYE MOVEMENTS. The second defining characteristic of VSNs is their discharge in relation to vestibular stimulation in the pitch plane. Forty-six VSNs were analyzed for vestibular-related discharge during sinusoidal pitch rotation in the dark. Figure 5 shows an example of this discharge for the same neuron illustrated in Fig. 3. When the animal was pitched in the dark (Fig. 5, A and B), VSN discharge was modulated; upward chair movement resulted in increased discharge and higher velocities resulted in deeper modulation (compare 0.25 Hz in Fig. 5A with 0.5

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Hz in Fig. 5B). To be certain that the sometimes modest modulation (A) was related to the vestibular stimulation and not, for example, to eye position, we tested VSNs during suppression (see METHODS). VSNs always were modulated during this condition, and the modulation was usually more robust than during VOR in the dark (compare Fig. 5, A and B with C and D).

The frequency response of the gain and phase relative to head position and head velocity were calculated independently with the least-squares sinusoidal fit (see METHODS). The results are shown in Fig. 6, along with the average gains and phases of the VOR in the dark, calculated by the same methods at the same time. Although the VOR remained constant (note the relatively flat gain and phase curves) over the frequencies tested, position sensitivity increased over the frequency range of 0.1–1.0 Hz (Fig. 6, top left) from 0.5 to nearly 4.0 spikes/s per deg for both the up VSN illustrated previously (triangles) and a typical down VSN (squares). In contrast, velocity sensitivity decreased for up VSNs from ~1.5 to 0.6 spikes/s per deg/s over the same frequency range. Down VSNs were more variable in this characteristic, so although the illustrated VSN (squares, Fig. 6, top right) showed some tendency to decrease its sensitivity at higher frequencies, down VSNs remained fairly constant at ~0.7 spike/s per deg/s. On average, the populations of up and down VSNs behaved identically to the two example neurons. VSNs discharged in phase with eye velocity (Fig. 6, bottom): up VSNs with upward eye velocity (indicated by near 0 phase shift, triangles and ×, bottom right) and down VSNs with downward eye velocity (indicated by 180° phase lag).

The average gain and phase from the least-squares fit sinusoids relative to chair position for all VSNs tested at 0.5 Hz during ±10° pitch in the dark were 2.13 ± 1.55 (SD) spikes/s per deg and 93.16 ± 35.99° phase lead for up VSNs and 2.12 ± 1.23 spikes/s per deg and −80.53 ± 38.00° phase lag for down VSNs. Those relative to chair velocity were 0.62 ± 0.44 spike/s per deg/s and 3.09 ± 35.96° phase lead for up VSNs and 0.62 ± 0.35 spike/s per deg/s and −170.57 ± 37.93° phase lag for down VSNs. During suppression, again for 0.5 Hz, ±10° sinusoidal pitch, the average gain and phase for the least-squares fit sinusoids relative to chair position were 3.29 ± 1.79 spikes/s per deg and 114.22 ± 63.78° phase lead for up VSNs and 2.21 ± 1.27 spikes/s per deg and −55.19 ± 70.00° phase lag for down.
FIG. 6. Gain and phase plots of VSN discharge as a function of frequency for all VSNs. *Top:* gain; *bottom:* phase calculated relative to chair position (*left*) or chair velocity (*right*). For comparison, the simultaneously computed VOR (*●*) is shown in each panel and is unitless, normally ranging from 0.5 to 1.0 in this and Fig. 7. Representative up (△, W 29:1) and down (□) VSNs are shown along with the averages for all up (×) and down (*) VSNs. Note that VSNs discharge in phase with either upward or downward chair velocity (*bottom right*).

As summarized in Fig. 6, up VSNs discharged in phase with upward chair velocity (i.e., near 0 phase) and down VSNs discharged for downward chair velocity (−180° phase). Figure 7 shows the distribution of gains and phases re velocity for rotation at 0.5 Hz, ±10°. The distribution of gains did not differ between up and down VSNs. Up VSNs were clustered around 0° phase and down around −180°. The aberrant phase lag of one up VSN (open bar between −135 and −180°, Fig. 7, *bottom right*) during suppression probably reflects the influence of eye velocity on the discharge during the suppression task (see SMOOTH-PURSUIT EYE MOVEMENTS). Unexpectedly, discharge sensitivity was higher (3.29 ± 1.79 spikes/s per deg relative to position and 0.97 ± 0.53 spike/s per deg/s relative to velocity) for up VSNs during suppression than for down VSNs during suppression or for either up or down VSNs during VOR in the dark (2.17 ± 1.29 spikes/s per deg relative to position and 0.64 ± 0.37 spike/s per deg/s relative to velocity).

**Maximum activation direction**

To assess whether the vestibular response was type I (ipsilateral excitatory input) or type II (contralateral) (Duensing
and Schaefer 1958; Shimazu and Precht 1965), we used a technique similar to MAD analysis introduced by Baker et al. (1984). By repositioning the animal in the yaw plane while continuously applying sinusoidal vertical rotation at our standard ±10°, we could move the ipsilateral anterior canal/contralateral posterior canal pair into a position of maximum or minimum activation to ascertain whether it or the opposite pair most likely supplied the vestibular input (Baker et al. 1984; Fukushima et al. 1995). Figure 8 shows the results of this procedure for our well-documented up VSN, W29:1. This neuron was recorded on the right side in phase with upward eye velocity and down VSNs were in lower half, bottom phase with downward eye velocity (see Fig. 8, bottom) as indicated by the positive values (Fig. 8, top). For this neuron, the least-squares fit sinusoid of the gain with respect to chair velocity (cf. chair position used by Baker et al. 1984) indicated a maximum gain for the fit at ~125° (fit for 0.25-Hz pitch), which is near the plane for the ipsilateral posterior canal (i.e., 135°). Thus this neuron was type I receiving excitatory input from the ipsilateral posterior canal.

Although we did not test VSNs at as many yaw positions, we did test 23 VSNs during VOR in the dark and 23 neurons during suppression of the VOR for at least ±90° yaw as well as normal pitch. We could calculate a MAD for VOR in the dark and/or during suppression conditions for 5 up and 16 down VSNs. Those MADs always showed a similar reversal of phase like that shown in Fig. 8; in particular, 9/21 VSNs showed reversal, indicating an ipsilateral MAD that suggests a type I vestibular response. Only 1/5 up VSNs was type II, whereas the majority (11/16) of down VSNs were type II.

**Fig. 8.** Maximum activation direction. Example of the maximum activation analysis (MAD) calculation for VSN W29:1 during suppression. Procedure was identical to that used by Baker et al. (1984) except that we used gain (*) and phase (●) for chair velocity, rather than position, because VSNs discharge in phase with velocity. Gain (top) and phase (bottom) were calculated for ±10 cycles of vertical rotation, ±10° at each of the indicated yaw positions. Gains were assigned a positive or negative sign on the basis of the phase (re: position) as in previous analyses (Baker et al. 1984; Fukushima et al. 1995). Note the abrupt shift in phase at ~30°–40° and the maximum gain at ~125°, suggesting input from the ipsilateral posterior canal for this up VSN. The illustrations are for 0.25 Hz.

**SMOOTH-PURSUIT EYE MOVEMENTS.** An example of pursuit-related discharge is shown in Fig. 9 (top) for VSN W29:1. Note that the discharge is modulated deeply during tracking of this ±10°, 0.5-Hz vertical target movement. When we varied the frequency of the target movement from 0.1 to 1.0 Hz, the gain and the phase of the pursuit tracking were quite constant (Fig. 9, bottom; diamonds). In contrast, the dynamic position sensitivity (K_p) of this VSN (triangles) as well as all up (squares) and down (×) VSNs increased, whereas velocity sensitivity decreased. Up VSNs discharged in phase with upward eye velocity and down VSNs were in phase with downward eye velocity (see lower half, bottom right).

The responses of 34 VSNs tested during sinusoidal smooth pursuit were quantified in a similar manner. The sensitivity (peak-to-peak VSN discharge/eye movement amplitude) and the phase lead (positive numbers) or lag (negative numbers) for target movements of 0.5 Hz, ±10° are presented in Fig. 10. All VSNs that discharged during upward chair movement also discharged for upward target tracking, and all down VSNs discharged during downward chair movement and downward pursuit. Nearly all VSNs discharged in phase with up or downward velocity, but one up VSN (W27:2) and two down (W29:4 and W12:1) VSNs showed phase relations that were intermediate between eye position and velocity. Although there was considerable variability among VSNs, on average they were nearly three times more sensitive (2.8 ± 3.1 relative to position, 2.9 ± 1.9 relative to velocity) during pursuit than during VOR in the dark. Because eye velocity is not controlled during VOR in the dark, a comparison of sensitivities during suppression with those during pursuit offers a more pure comparison of the relative strengths of the vestibular and pursuit-related discharge. Figure 11A shows the sensitivities in each condition taken at 0.5 Hz, ±10° plotted against each other for the 28 VSNs recorded during both conditions. The thin gray line...
FIG. 9. Sinusoidal smooth-pursuit-related VSN discharge. *Top*: averaged pursuit-related discharge for VSN W 29:1. Traces are (top to bottom) HE; VT; VE; VT, vertical target velocity; VE, vertical eye velocity; firing rate, the average histogram for the discharge; and individual rasters. Note clear, significant modulation in phase with upward eye velocity. Conventions as in Fig. 5. Below, gain and phase plots for VSN discharge as a function of frequency. Key at right applies to all 4 panels and is the same as in Fig. 6.

has a slope of 1.0 to indicate the expected distribution if the sensitivities were equal. One VSN was most sensitive to vestibular input, three had nearly equal sensitivities, and 24/28 (86%) showed higher pursuit than vestibular sensitivity.

The fact that VSNs discharge for vestibular and smooth-pursuit movement in the same direction could explain the low gain of some VSNs during VOR in the dark, as the different sensitivities should reduce the discharge because the eye velocity sensitivity is 180° out of phase with the vestibular input. However, a rough comparison of sensitivities for the various conditions suggested that the responses during suppression and pursuit are not added linearly to yield the response during VOR in the dark. For example, our well-documented VSN (W 29:1) discharged in phase with both upward chair velocity during suppression and upward eye velocity during smooth pursuit. The suppression gain was ~0.6 spike/s per deg/s and pursuit sensitivity was 2 spikes/s per deg/s, so linear addition of the antagonistic responses might be expected to produce a gain of ~1.4 spikes/s per deg/s for VOR in the dark. Instead, the gain averaged ~0.7 spike/s per deg/s.

To test for possible linear summation more quantitatively, it would have been necessary to record VSN activity during pitch while the animal fixated a target that was stationary in space. Discharge during that condition then could be compared with that predicted by summing the sensitivities during pursuit and pitch alone. Unfortunately, we could not test VSNs easily in this procedure because of equipment limitations. Instead, we devised an estimate of the additivity of the pursuit and pitch sensitivities by comparing the expected combined responses with the value for VOR in the dark that was corrected for uncontrolled eye movements. Discharge during VOR in the dark was taken at 0.5 Hz, ±10° pitch and corrected by adding the discharge due to eye movement...
estimated on the basis of its smooth-pursuit sensitivity multiplied by the gain of the VOR with respect to eye velocity. Average values were used if more than one series of a particular condition was recorded. This value was compared with values obtained by vector addition of the discharge during pursuit and pitch at the same amplitude and frequency. In Fig. 11B, each VSN that was recorded in all three conditions is represented by a single point. The corrected discharge during VOR in the dark (actual modulation) divided by the vector addition of the independent discharge sensitivities during pitch and pursuit (predicted modulation) is plotted on the ordinate. They are positioned along the abscissa according to the difference in the phase (actual-predicted) where the predicted phase is again estimated from the vector sum of pursuit and suppression. Down VSNs (dots) ranged from 59 to 246° phase lag with a cluster near the 180° lag position (light vertical line; average 110° ± 81°). Up VSNs ranged from 125° lead to 15° lag and clustered near the 0° phase. In addition, the points distribute beneath the line of ratio 1.0 (light horizontal line) that indicates equal actual and predicted modulations. The average ratio was 0.78 ± 0.22. Thus although the pursuit-related and pitch-related discharges do not appear to add strictly linearly on average, they do not combine in a drastically nonlinear fashion.

To further corroborate the surprising pursuit-related discharge, we tested an additional five VSNs during vertical step-ramp pursuit (Rashbass 1961). All five showed pursuit-related discharge during constant-velocity ramp tracking, and the discharge was proportional to the target velocity.

**Medullary recordings**

In sharp contrast to findings in cats (Kitama et al. 1992a,b, 1995; Ohki et al. 1988), we could not locate any neurons that discharged like cat BDNs in the rostral medullas of monkeys Z and M. In particular, we searched for neurons that discharged for contralateral saccades and received vestibular input as judged by their discharge modulation during vestibular stimulation, especially during suppression. In monkey Z, we identified the region of the nucleus prepositus hypoglossi, adjacent medial vestibular nucleus, and underlying reticular formation by the characteristic discharge of the neurons of that region and their position relative to the abducens nuclei.

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**Fig. 10.** Frequency histograms of gains (left) and phases (right) for smooth-pursuit sensitivity in all VSNs. Top: relative to eye velocity. Bottom: relative to eye position. □, up VSNs; ●, down VSNs.

**Fig. 11.** Comparison of discharge sensitivities. A: vestibular sensitivity during suppression (ordinate) is plotted against pursuit sensitivity for up (□) and down (●) VSNs. Note that most fall below the line of equal sensitivity (thin gray line). B: summation of discharge sensitivities. Ratio of actual to predicted modulation (ordinate) is plotted against actual minus predicted phase (abscissa). See text for details.
(Kaneko 1997). This animal had 283 separate tracks run during a 44-mo period. In *monkey M*, we systematically tracked a 0.5-mm grid that extended from the caudal margin of the abducens nuclei 4.0 mm posteriorly and ±2.5 mm lateral of midline to a depth of 4.0 mm below the floor of the fourth ventricle. We explored every 0.5-mm position along the grid at least once and repeated any positions associated with poor recording conditions or possible BDN-like neurons.

In no instance did we find neurons that elicited a burst of action potentials for contralateral saccades and were excited by yaw rotation to the side contralateral to the recording side. Most of the neurons that showed prominent saccade- and vestibular-related discharge were identical to those described by McFarland and Fuchs (1992), some of which are like the VSNs described earlier. As far as we could tell, all saccade-related activity showed excitatory bursts for ipsilateral but not contralateral saccades, although for tracks near the midline, it was sometimes difficult to be certain which side was being recorded. However, no peri-midline tracks yielded neurons with saccade- and vestibular-related discharge, so identification of putative BDNs was not a problem. We are quite confident that we did not miss BDN-like neurons because of the ease with which we located and identified VSNs in the mesencephalon (see INC recordings) using identical techniques that should have identified such neurons easily.

**DISCUSSION**

Vertical VSNs in the region of the INC form a compact, uniform group that is distinctive from other oculomotor nuclei that have been described in the region (Fig. 1). The area is dorsolateral to the oculomotor nucleus, medial and dorsal to the saccade-related neurons of the central mesencephalic reticular formation (e.g., Waitzman et al. 1996), and caudal and dorsal of the rostral interstitial nucleus of the medial longitudinal fasciculus (Büttner-Ennever 1977), which contains vertical excitatory burst neurons. Thus VSNs form a distinct anatomic group of saccade-related neurons. Although they might have included some of the burst-tonic neurons described by King et al. (1981), they were quite different quantitatively and qualitatively from burst-tonic neurons, which discharged very little during suppression, and from irregular tonic neurons, which did not burst for saccades (King et al. 1981).

The saccade-related discharge of our VSNs was quite variable and poorly related to the metrics of the saccade. In fact, their discharge was no better related to saccades than that of their feline counterparts even though the relation between saccade metrics and the discharge of saccade-related neurons is normally tighter in monkeys than in cats (see Moschovakis et al. 1996 for review). Not only were the correlations comparatively poor, but the discharge sensitivity of VSNs was lower than for many other types of neurons. For example, the slope of the numbers of spikes/size relation yields an average sensitivity (slope) of 0.27 spike/deg, which is about five times less than that of simian vertical excitatory burst neurons (~1.33 spikes/deg) (King and Fuchs 1979) and four times less than that of BDNs (Kitama et al. 1995). Because monkeys lack horizontal VSNs and the discharge of vertical VSNs is not well related to saccades, it seems unlikely that their VSNs participate in any substantive way in the generation of saccades.

Similarly, the eye-position sensitivity of VSNs is inconsistent. We could not demonstrate a static position sensitivity ($K_v$) in untrained cats (Fukushima et al. 1995), and the present results show that it is poor in monkeys. VSNs had $K_v$ values of <1 spike/s per deg (mean 0.55 ± 0.47). In contrast, their most similar counterpart in the horizontal system, medullary eye/head velocity neurons ($\hat{E}/\hat{V}$), are three times more sensitive (McFarland and Fuchs 1992) and motoneurons are at least five times more sensitive (e.g., Robinson 1970). The low position sensitivity, the occasional discordance between that sensitivity and the on-direction for the VSN, and the lack of statistically significant position sensitivity in half of the VSNs all suggest that VSNs cannot contribute a substantial eye-position command to nearby oculomotor structures. In this regard, they are quite different from the vertical motoneurons and the contralateral INC neurons that participate in the vertical neural integrator (see Fukushima and Kaneko 1995 for discussion). This result contrasts sharply with findings for burst-tonic neurons (King et al. 1981), which display high correlations (average = 0.95) between discharge and eye position and slopes ($K_v$) of that relation that are several times (average = 2.6 spikes/s per deg) larger than our values. It is also consistent with our surmise that VSNs are closer to the input than the output of the vertical neural integrator.

In contrast, the vestibular input to VSNs is quite robust, showing substantial sensitivity to chair position and velocity (Figs. 5–7). Because VSNs discharged in phase with either upward or downward chair movement over the frequency range tested (Fig. 6), they apparently are related most closely to head velocity. Although they discharged more vigorously during suppression than VOR in the dark (Fig. 5), the robust responses during the latter condition suggest that an eye-movement component contributed substantially to their discharge during VOR in the dark. The slight differences in phase estimated during the two conditions are not statistically significant but may reflect the contribution of eye movement to suppression. Up VSNs showed a slightly higher vestibular sensitivity than down VSNs, just as they did in cats (Fukushima et al. 1995).

The overall average discharge sensitivity (slightly <1 spike/s per deg/s relative to velocity) for monkey VSNs is less than that of their feline counterparts (2–3 spikes/s per deg/s relative to velocity) but is similar to simian $\hat{E}/\hat{V}$ neurons (1.1 spikes/s per deg/s) (McFarland and Fuchs 1992). Unlike $\hat{E}/\hat{V}$ neurons (McFarland and Fuchs 1992), VSN dynamic position sensitivity ($K_v$) increased fourfold over the range tested and showed a constant phase over frequency. The increasing $K_v$ and decreasing velocity sensitivity ($R_v$) of VSNs yielded a decreasing time constant (velocity gain/position gain) that fell smoothly from ~1.3 s at 0.125 Hz and leveled off at 0.2 s at 0.5 Hz to asymptote near 0.15 s at 1.0 Hz. The decreasing $R_v$ is similar to that first reported for abducens motoneurons (Fuchs et al. 1988). As $\hat{E}/\hat{V}$ neurons also show a similar declining $R_v$, it seems that this characteristic of motoneuron discharge may be found generally and is not attributable to a single motoneuron input. Similarly, the $K_v$ is much larger than that estimated during fixa-
tion just as it was for motoneurons and $E/V$ neurons (Fuchs et al. 1988; McFarland and Fuchs 1992), but the difference is much larger in VSNs and increases substantially at higher frequencies. Thus it seems less likely that this characteristic is solely attributable to the need to match the dynamics of the eye mechanics (cf. Fuchs et al. 1988); rather, it may reflect additional functions that VSNs serve. One possible additional function is neural integration of velocity signals from oculomotor subsystems.

The distribution of MADs was based on limited data but it showed both similarities to and differences from our data on cats (Fukushima et al. 1995). Whereas most down VSNs receive input from the contralateral anterior canal in both cats and monkeys, about one-third of monkey VSNs (vs. none in cats) apparently receive predominant input from the ipsilateral anterior canal and are therefore type I. Up VSNs receive input from both the ipsilateral (type I) and contralateral (type II) posterior canals in both cats and monkeys, but they are predominantly type I in monkeys and type II in cats.

A surprising finding of this study was the smooth-pursuit sensitivity of VSNs. Cats have very rudimentary pursuit capabilities, and it is exceedingly difficult to train them to track a small target spot, so even if pursuit sensitivity is present, it is unlikely to be very significant. In our monkeys, pursuit sensitivity was most obvious at higher frequencies and decreasing velocity sensitivity was somewhat offset by increasing position sensitivity, so the pursuit-related discharge was not immediately obvious because it seemed not to vary with stimulus frequency. Nonetheless, when tested with sinusoidal target movements, pursuit-related discharge showed that depending on the paradigm, VSNs were two to six times more sensitive to smooth-pursuit eye movements than to vestibular stimulation. This pursuit-related discharge was not a function of the paradigm, because VSNs showed similar activity during step-ramp tracking. The pursuit discharge was also not due to visual input because there was no retinal-slip–related discharge in the several VSNs tested, the pursuit-related discharge was bidirectional unlike the BDN visual response, and the low target velocities consistently yielded pursuit-related discharge. Although VSNs discharged roughly in phase with eye velocity, the peak discharge sometimes led peak eye movement so that some VSNs could participate in the generation of smooth pursuit. However, VSN discharge usually was inhibited at the beginning of ramp pursuit and did not increase with higher accelerations so it is unlikely that VSNs participate in the initiation phase of pursuit.

The time constant ($R/K_d$) for smooth pursuit decreased in parallel with that for vestibular-related discharge even though the absolute gains were three times as high. They both fell from $\sim 1.2$ s at 0.125 Hz to asymptote near 0.15 s at 1.0 Hz. $R$ decreased with increasing frequency as it does for motoneurons (Fuchs et al. 1988), and $K_d$ increased over the frequencies tested, doubling instead of tripling as it did for vestibular-related discharge, perhaps owing to the initial higher gain for pursuit. The $K_d$ calculated for smooth pursuit was even more disparate from that calculated for periods of fixation because of the higher pursuit gain. The increasing $R$ corroborates the findings for VSN vestibular sensitivity, and the identical frequency response of the time constant suggests that VSNs process vestibular and eye velocity signals similarly.

Because the pursuit and vestibular sensitivities are not linearly additive (Fig. 11B), the gain during VOR in the dark (vestibular plus eye movement) could not be predicted from the response to pure vestibular stimulation (suppression) and the response to pure eye movement (pursuit). This finding is identical to that for $E/V$ neurons (McFarland and Fuchs 1992) and distinguishes these neurons from gaze velocity neurons (e.g., Lisberger and Fuchs 1978), in which the two sensitivities do add linearly.

Perhaps the most surprising result of this study was the failure to find neurons similar to the horizontal BDNs found in the homologous region in cats. The discharge characteristics and location of BDNs are well documented in cats (Kimata et al. 1992a,b, 1995; Ohki et al. 1988), and a central role in the production of saccades has been postulated on the basis of their saccade-related discharge, their projection to the region of the contralateral excitatory burst neurons, and their direct input from the superior colliculus. We are quite certain that we surveyed the homologous region completely in monkeys $Z$ and $M$. We also are sure that we did not miss any BDNs due to technical shortcomings because of the ease with which we could find and characterize VSNs that required similar techniques. It is possible that there may be actual differences between cats and monkeys in the way saccades are programmed. Such differences would be consistent with the quantitative differences in the metrics of saccades, the discharge of burst generator neurons, and the differences in normal orienting behavior seen between the two species (see Moschovakis et al. 1996 for a recent review). Another possibility is that alternative functions of cat BDNs, such as generation of quick phases during nystagmus (Kimata et al. 1995), may be mediated by vestibular plus saccade neurons (Fuchs and Kimm 1975) or more laterally located neurons in the monkey.

We conclude that VSNs are not important for saccade generation in the monkey because VSNs with horizontal on-directions do not seem to exist and because the discharge metrics of vertical VSNs are not well related to the metrics of vertical saccades. We suggest that the evidence to date favors a role in the neural integration of vestibular, saccadic, and smooth-pursuit signals into position-coded output that helps maintain vertical gaze position. The fact that VSN discharge is usually nearly in phase with velocity suggests that they lie on the input side of the network that produces neural integration (Robinson 1975, 1989). In recent models, the neural integrator is thought to be composed of layers of neurons because the layering yields more rapid distribution of the eye-position signal throughout the integrating network and enables the inclusion of an eye-velocity component as seen in real neurons (see Cannon and Robinson 1985 for discussion). The input layer should mimic more closely the velocity-related discharge of its sources in contrast to the output, which is eye position. While a similar functional role may be subserved by $E/V$ neurons in the monkey horizontal system (McFarland and Fuchs 1992), the increase of $K_d$ with frequency places $E/V$ neurons closer to the output of the neural integrator than VSNs because their discharge resembles that of motoneurons.
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Address for reprint requests: C.R.S. Kaneko, Regional Primate Research Center, Box 357330, University of Washington, Seattle, WA 98195.

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