

The nucleus prepositus predominantly outputs eye movement-related information during passive and active self-motion

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Dale A, Cullen KE. The nucleus prepositus predominantly outputs eye movement-related information during passive and active self-motion. *J Neurophysiol* 109: 1900–1911, 2013. First published January 16, 2013; doi:10.1152/jn.00788.2012.—Maintaining a constant representation of our heading as we move through the world requires the accurate estimate of spatial orientation. As one turns (or is turned) toward a new heading, signals from the semicircular canals are relayed through the vestibular system to higher-order centers that encode head direction. To date, there is no direct electrophysiological evidence confirming the first relay point of head-motion signals from the vestibular nuclei, but previous anatomical and lesion studies have identified the nucleus prepositus as a likely candidate. Whereas burst-tonic neurons encode only eye-movement signals during head-fixed eye motion and passive vestibular stimulation, these neurons have not been studied during self-generated movements. Here, we specifically address whether burst-tonic neurons encode head motion during active behaviors. Single-unit responses were recorded from the nucleus prepositus of rhesus monkeys and compared for head-restrained and active conditions with comparable eye velocities. We found that neurons consistently encoded eye position and velocity across conditions but did not exhibit significant sensitivity to head position or velocity. Additionally, response sensitivities varied as a function of eye velocity, similar to abducens motoneurons and consistent with their role in gaze control and stabilization. Thus our results demonstrate that the primate nucleus prepositus chiefly encodes eye movement even during active head-movement behaviors, a finding inconsistent with the proposal that this nucleus makes a direct contribution to head-direction cell tuning. Given its ascending projections, however, we speculate that this eye-movement information is integrated with other inputs in establishing higher-order spatial representations.

prepositus; heading; active motion

THE NUCLEUS PREPOSITUS HAS been associated with a number of important functions (Fig. 1A). First, based on its projections to the extraocular motor nuclei and areas of the reticular formation [monkey: Belknap and McCrea (1988), Robinson et al. (1994); cat: Langer et al. (1986), McCrea and Baker (1985); rat: Iwasaki et al. (1999)], it is implicated in premotor control of both saccades and pursuit eye movements. Second, the nucleus prepositus also sends efferent projections to several brain areas that mediate the vestibulo-ocular reflex (VOR) and optokinetic nystagmus, including the vestibular nuclei and inferior olive [monkey: Belknap and McCrea (1988), Carleton and Carpenter (1983); cat: McCrea and Baker (1985); rabbit: Arts et al. (2000), Barmack et al. (1993)], and thus is thought to play a vital role in gaze stabilization. Finally, the nucleus

prepositus sends projections to the dorsal tegmental nucleus [rat: Brown et al. (2005); Cornwall et al. (1990); Liu et al. (1984)], a structure that has reciprocal connections with the lateral mammillary nuclei (LMN). In turn, the LMN comprise head-direction cells in rodents and are part of the classic Papez circuit [reviewed in Taube (1998); Wiener et al. (2002)]. Thus based on these connections, the role of the nucleus prepositus has also been linked to spatial perception.

Neurophysiological and lesion experiments have provided strong evidence to support that the nucleus prepositus makes a major contribution to the first two of these important functions. In particular, single-unit recordings have revealed that the majority of its neurons encodes ipsilateral eye-position and -velocity signals during fixation (i.e., between saccades) and smooth pursuit and produces a burst of action potentials for ipsilateral saccades [monkey: Cullen et al. (1993), McFarland and Fuchs (1992), Sylvestre et al. (2003); cat: Escudero et al. (1996), Lopez-Barneo et al. (1982)]. This result implies that activity in the nucleus prepositus provides an essential drive to extraocular motoneurons during fixation and pursuit and also contributes to the generation of saccadic eye movements. Further support for this idea is provided by studies showing that localized lesions produce eye-position drifts toward the center, especially following ipsilateral saccades [monkey: Cannon and Robinson (1987), Kaneko (1997); cat: Cheron et al. (1986a)], demonstrating a loss of eye-position and -velocity control. Additionally, single-unit recordings and lesion studies have provided support for the second proposal, namely, that the nucleus prepositus plays a vital role in gaze stabilization. Notably, prepositus neurons encode eye movement-related information during the VOR [monkey: Cullen et al. (1993), McCrea and Cullen (1992), McFarland and Fuchs (1992); cat: Escudero et al. (1996), Lopez-Barneo et al. (1982)], and localized lesions produce quick-phase asymmetries and deficits in slow-phase velocity during the VOR and optokinetic stimulation [monkey: Kaneko (1999); cat: Cheron et al. (1986a, b)].

In contrast, neurophysiological evidence is lacking in support of the proposal that the nucleus prepositus makes a major contribution to spatial perception. Its afferent inputs, however, include direct, bilateral projections from the vestibular nuclei [monkey: McCrea et al. (1987); cat: McCrea and Baker (1985); rat: Brown et al. (2005)]. Importantly, McCrea et al. (1987) found that specific neurons in the vestibular nuclei, termed position-vestibular-pause neurons, project directly to and terminate on nucleus prepositus neurons. Position-vestibular-pause neurons consistently encode both eye and head motion during active as well as passive movements to stabilize gaze [reviewed in Cullen and Roy (2004)]. As such, the efferent

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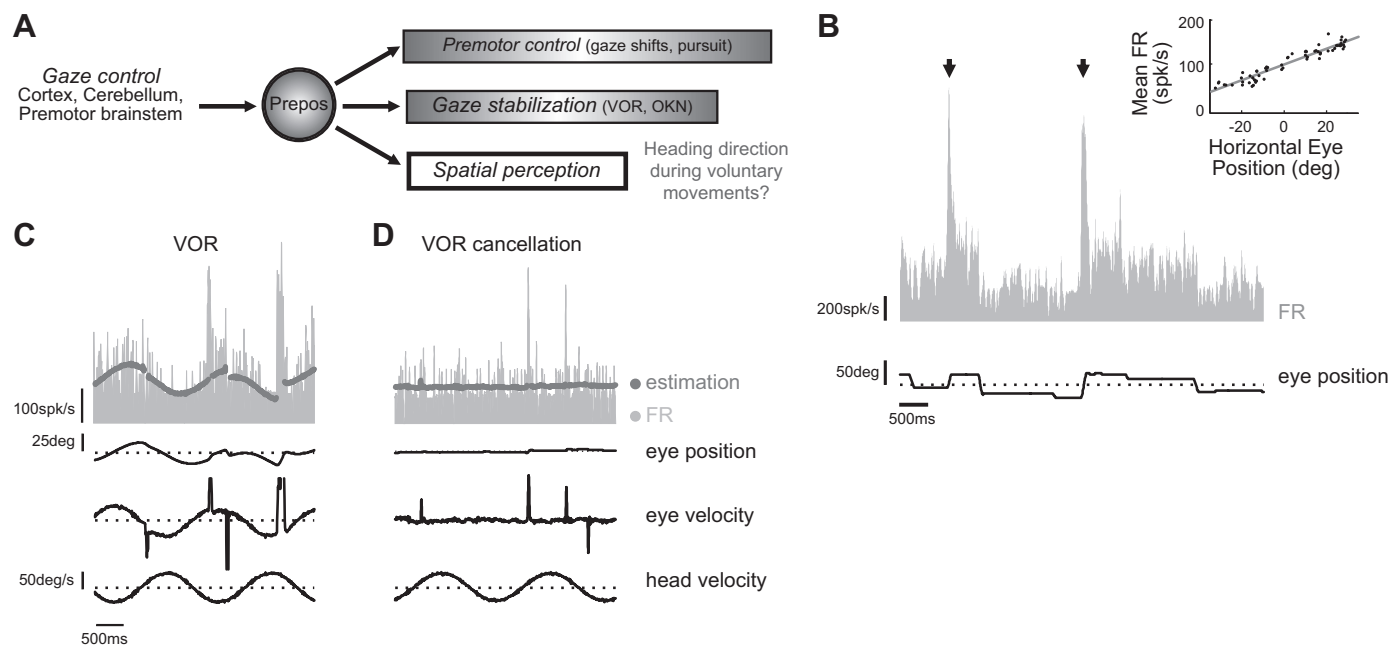


Fig. 1. *A*: functional roles of the nucleus prepositus (Prepos) based on anatomical studies. Its role, addressed in this study, is shown in the bolded box. VOR, vestibulo-ocular reflex; OKN, optokinetic nystagmus. *B*: characteristic burst-tonic response of example neuron OR5000 during head-fixed saccades (arrows indicate ipsilateral saccades) and fixation. *Inset*: firing rate (FR) vs. eye position for fixation; the slope of the linear regression (solid line) corresponds to eye-position sensitivity. $R^2 = 0.91$. spk/s, spikes/s. *C*: the example neuron's response during VOR and (*D*) VOR cancellation. Dark gray traces represent firing-rate prediction based on model coefficients estimated during smooth pursuit (see Fig. 2). Traces toward the top of the page correspond to the neuron's ipsilateral direction.

projections of prepositus may be consistent with providing head motion-related information to the head-direction cell network. Nevertheless, a direct and specific demonstration of this contribution still has yet to be obtained.

Accordingly, in the present study, we used electrophysiological experiments to establish whether the nucleus prepositus encodes signals related to spatial perception. To date, the activity of burst-tonic prepositus neurons has been characterized only during head-restrained, passive motion, a condition during which it is known exclusively to encode eye movements (Cullen et al. 1993; McCrea and Cullen 1992; Sylvestre et al. 2003). These results appear at odds with the proposal that the nucleus prepositus provides head-position information to the dorsal tegmental nucleus and in turn, to the head-direction pathway [reviewed in rat in Taube (2007)]. However, Bassett and Taube (2001) proposed that the nucleus prepositus plays a role in updating head-direction cell signals during self-generated motion when it is particularly important for the brain to maintain an estimate of heading. Thus we recorded the activities of individual burst-tonic prepositus neurons in rhesus monkeys while the monkeys changed their head position by producing voluntary head movements. We specifically tested whether individual neurons in the nucleus prepositus reliably encode head motion by comparing responses during eye motion in head-restrained conditions with responses generated when large, active head movements were made in conjunction with eye movements. Our results show that the nucleus prepositus predominantly encodes eye movement during active as well as passive head motion. We suggest that this eye-related information is combined with head-related inputs from other sources by higher-order centers that contribute to spatial perception.

METHODS

All experimental procedures were approved by the McGill University Animal Care Committee and in compliance with the guidelines of the Canadian Council on Animal Care.

Surgical Procedures

Two rhesus monkeys (*Macaca mulatta*) were prepared for acute extracellular recording experiments using aseptic surgical techniques. Fifteen minutes preoperatively and every 2.5–3 h during surgery, animals were injected with the anticholinergic glycopyrrolate (0.005 mg/kg im) to stabilize heart rate and to reduce salivation. Animals were then pre-anesthetized using ketamine hydrochloride (15 mg/kg im). Finally, buprenorphine (0.01 mg/kg im) and diazepam (1 mg/kg im) were injected as an analgesic and to provide muscle relaxation, respectively.

Loading doses of dexamethasone (1 mg/kg im) and cefazolin (50 mg/kg iv) were administered to reduce swelling and prevent infection, respectively. Surgical levels of anesthesia were then achieved using isoflurane gas, maintained at 0.8–1.5%, together with a minimum 3 l/min (dose adjusted to effect) of 100% oxygen. Heart rate, blood pressure, respiration, and body temperature were monitored throughout the procedure.

A stainless-steel post was chronically fastened to each animal's skull with stainless-steel screws and dental acrylic to allow complete immobilization of the animal's head during experiments. A stainless-steel recording chamber was also fastened with dental acrylic to the implant and positioned to provide access to the nucleus prepositus, oriented at 30° and 26° posterior and lateral angles, respectively. Craniotomy was performed within the recording chamber to allow electrode access to the brain stem. Finally, an 18-mm-diameter eye coil (three loops of Teflon-coated stainless-steel wire) was implanted in one eye behind the conjunctiva (Fuchs and Robinson 1966).

After surgery, dexamethasone (0.5 mg/kg im; for 4 days) administration was continued. Buprenorphine (0.01 mg/kg im) was given as

postoperative analgesia every 12 h for 2–5 days, depending on the animal's pain level, and anafen (2 mg/kg and then 1 mg/kg on subsequent days) was used as an anti-inflammatory. In addition, cefazolin (25 mg/kg) was injected twice daily for 10 days. Animals recovered for 2 wk before any experimenting began.

Behavioral Paradigms

Experimental setup. During recordings, monkeys were seated comfortably in a primate chair that was mounted on a vestibular turntable in the center of a 1-m³ magnetic field coil (CNC Engineering, Enfield, CT). All neurons were recorded initially during head-restrained behavioral paradigms to characterize their sensitivities to eye movements and/or passively applied head velocity. Monkeys were trained, with juice reward, to follow a red helium–neon laser that projected onto a cylindrical screen located 55 cm from their eyes. Target position and turntable velocity were controlled using REX, a QNX-based, real-time data acquisition system (Hayes et al. 1982).

Head restrained. Saccadic eye movements were elicited by unpredictably stepping the laser target between horizontal positions $\pm 30^\circ$ in 5° subdivisions. Slow velocity, smooth eye movements were then elicited in two separate paradigms: 1) smooth pursuit following sinusoidal target motion (0.5 Hz, peak velocity 40 and 60°/s) and 2) VOR during sinusoidal, passive, whole-body rotations about an earth-vertical axis (0.5 Hz, peak velocity 40°/s) in the dark. Neuronal sensitivities to head velocity were tested by rotating the monkeys while they followed a laser target that moved with the vestibular turntable [VOR cancellation (VORc); 0.5 Hz, peak velocity 40°/s]. Finally, monkeys generated VOR in the dark in response to passive, whole-body rotations that mimicked the trajectory of a 60° head-unrestrained gaze shift with peak velocity 200°/s (active-like VOR), thereby generating intermediate eye velocities.

Head free. After a neuron was tested in the head-restrained condition, the monkey's head was released slowly and carefully to maintain isolation. Once released, the monkey was able to rotate its head about the earth-vertical axis. Active behavioral paradigms were designed to encourage the production of large, voluntary head movements accompanied by eye movements with comparable velocities to those produced in the head-restrained condition. The monkeys performed 1) smooth eye-head pursuit following sinusoidal target motion (0.5 Hz, peak velocity 60 and 80°/s) and 2) gaze shifts between targets alternately presented at $\pm 30^\circ$, which consisted of a saccadic component and a subsequent gaze-stabilization component, characterized by intermediate eye velocities.

Data Acquisition

Behavioral signals. Gaze and head position were measured using the magnetic search-coil technique (Fuchs and Robinson 1966; Judge et al. 1980). Gaze-, head-, and target-position signals were low-pass filtered at 250 Hz and acquired at 1 kHz sampling frequency.

Neuronal recording. Extracellular single-unit activity was recorded using enamel-insulated tungsten microelectrodes (2–10 M Ω impedance; FHC, Bowdoin, ME). Electrodes were positioned using a two-dimensional coordinate system (Narishige International USA, East Meadow, NY), affixed to the recording chamber, and inserted into the brain within a 20-G guide tube. We located the abducens nucleus based on the characteristic discharge of its neurons (resembling a “singing beehive” sound) during spontaneous eye movements (Fuchs and Luschei 1970; Robinson 1970). We then mapped the nucleus' anterior-posterior and medial-lateral boundaries, verifying that its center comprised at least 2 mm of this characteristic activity along a single-recording track. All of the prepositus neurons in this study were then identified at a location 3.5–6.5 mm posterior to the center of the abducens nucleus, which assured that they were not part of the abducens nucleus.

When each neuron was isolated properly, extracellular potential and gaze-, head-, and target-position signals were recorded on digital audio tape for later playback, during which individual action potentials could be discriminated by a windowing circuit (BAK Electronics, Mount Airy, MD) and time stamped to generate a binary vector of unit activity. For analysis, the signals were imported into the Matlab (MathWorks, Natick, MA) programming environment. Behavioral signals were digitally filtered at 125 Hz, and eye position was computed as the difference between gaze and head. Eye, gaze, and head positions were then digitally differentiated to obtain velocity signals. Finally, estimates of neuronal firing rate were created by convolving a Gaussian function (SD of 10 ms for slow eye-velocity paradigms and 5 ms for intermediate and fast eye-velocity paradigms) with the unit activity.

Data Analysis

Head-fixed characterization during eye movements. All neurons were selected initially based on their increased modulation to ipsilaterally directed eye position and eye velocity. The onsets and offsets of head-fixed saccades were determined using a 20°/s velocity criterion. To determine each neuron's eye-position sensitivity, we considered epochs of ocular fixation of at least 300-ms duration, occurring no less than 50 ms following the end of spontaneous saccades; horizontal eye-position sensitivity was reported as the slope of a linear regression between mean firing rate and fixation position during at least 40 epochs. Dynamic linear optimization methods described previously (Sylvestre and Cullen 1999) were then used to quantify each neuron's sensitivity to eye movements during 1) ~ 10 cycles of smooth pursuit from which corrective saccades were excluded and 2) ≥ 20 ipsilaterally directed head-fixed saccades. The specific linear models used for these and subsequent analyses are described in RESULTS (Eqs. 1 and 2). A dynamic lead time (t_d), representing the time by which firing rate preceded saccade onset, was computed, as described by Sylvestre et al. (2003), and then used for all subsequent analyses of firing rate during rapid eye movements. Note that estimated coefficients are reported as positive for firing rates that increase for movements in the direction ipsilateral to the side of the recorded neuron. For each optimized model fit, we report the estimated coefficients as well as the variance accounted for $\{\text{VAF} = 1 - [\text{var}(\widehat{FR} - fr)/\text{var}(fr)]\}$, where \widehat{FR} is modeled firing rate, and fr is the recorded firing rate. A VAF of one indicates a perfect fit to the data, and zero indicates a fit that is equivalent to the neuron's mean firing rate.

Dynamic analysis during passive and active head motion. We confirmed each neuron's lack of head-position and -velocity sensitivity during passive vestibular stimulation by assessing the ability of Eq. 1 to predict the activity of each neuron during VOR and VORc. In addition, we used this same dynamic model of firing rate to describe neuronal responses during our “active-like” VOR paradigm described above. For our analysis of responses evoked in this condition, we quantified each neuron's firing rate during ~ 15 active-like head rotations toward the contralateral direction (i.e., rotations that produced ipsilaterally directed eye velocities).

To quantify neuronal responses during active head movements, we considered the following active behaviors: 1) ~ 10 cycles of eye-head pursuit, 2) ≥ 20 ipsilaterally directed gaze shifts, and 3) head movements generated while gaze was stable following ≥ 20 contralaterally directed gaze shifts (i.e., movements during which ipsilaterally directed VOR eye movements were generated). The goodness of fit of all estimates and predictions was quantified using VAF to allow direct comparison with head-fixed and passive responses.

Analysis of model coefficients. For each model coefficient computed in the analysis of neuronal responses during self-generated head motion, 95% bootstrap confidence intervals were computed (Carpenter and Bithell 2000) (see RESULTS). Briefly, 1,999 “new data sets” were generated by randomly sampling with replacement from the

original behavioral segments. Coefficient values were estimated for the 1,999 iterations, and distributions were obtained for each model coefficient.

To assess the relative strengths of eye vs. head encoding by individual neuronal responses, we computed head-motion coding indices for position and velocity. Each coefficient was calculated as the ratio of the head-related coefficient to the corresponding eye-related coefficient (i.e., position indices = head-position coefficient/eye-position coefficient, and velocity indices = head-velocity coefficient/eye-velocity coefficient). Notably, the values used for each coefficient were the means of their respective distributions, unless the 95% confidence interval overlapped zero, in which case, the coefficient was not statistically significant, and zero was used (Carpenter and Bithell 2000).

Unless otherwise noted, values are reported as mean \pm SD. Levels of significance were calculated using two-tailed Student's *t*-tests.

Confirmation of neuronal isolation. To confirm that isolation of the same neuron was maintained before and after the head-restrained/head-unrestrained transition, resting discharge rates (response with the eye centered) and eye-position sensitivities, while the monkey was still, were compared. If eye-related responses changed (or were lacking), indicating that the original neuron had either been lost or damaged in the transition between recording conditions, then the neuron was not included in our sample.

RESULTS

The goal of this study was to establish whether neurons in the primate nucleus prepositus contribute to head-motion signaling. To address this question, we first characterized the firing rates of single neurons while monkeys generated eye movements in the head-restrained condition (i.e., ocular fixation, pursuit, saccades, and the VOR). We then released the head to record the activity of the same neurons in the head-unrestrained condition while monkeys made voluntary head movements to orient to targets by producing eye-head pursuit and gaze shifts. We next assessed whether an eye movement-based model that optimally described a given neuron's activity for eye movements made in the head-restrained condition could be used to accurately predict its firing rate throughout the voluntary head movements. Finally, to explicitly quantify the significance of eye- vs. head-motion coding for each neuron, we used a nonparametric bootstrapping approach to estimate distributions of values for coefficients in a complete eye- and head-based model of firing rate during active movements.

Dynamic Analysis During Head-Restrained Eye Movements

The firing rates of all of the prepositus neurons recorded in this study ($n = 43$) were robustly modulated by ipsilateral eye position and eye velocity during head-restrained conditions, consistent with prior characterizations of prepositus burst-tonic neurons (McCrea and Cullen 1992; McFarland and Fuchs 1992). Figure 1, *B–D*, shows the responses of a typical neuron while the monkey generated eye movements in the head-restrained condition: the neuron fired a burst of action potentials for ipsilaterally directed saccades and sustained tonic firing rates that varied linearly with eye position (Fig. 1*B*). Furthermore, the same neuron's firing rate was strongly modulated by VOR (Fig. 1*C*); however, when the monkey cancelled its VOR by fixating a target that moved with its head during identical passive rotation (VORc), the neuron's firing rate remained constant (Fig. 1*D*). Accordingly, comparison of neuronal responses between the VOR and VORc conditions

confirmed that our sample of neurons did not respond to passively applied head motion but rather, encoded only eye-movement information.

To quantify the eye-movement sensitivity of a given neuron, we used a VAF criterion to determine the best fit with a dynamic model containing eye-position and -velocity terms

$$\widehat{FR}(t) = b + kE(t - t_d) + r\dot{E}(t - t_d) \quad (1)$$

where $\widehat{FR}(t)$ is the neuron's estimated instantaneous firing rate. We found the optimal-bias (b_s), eye-position (k_s), and eye-velocity (r_s) coefficients to describe each neuron's firing rate. Figure 2*A* shows that this model properly describes the firing rate of prepositus neurons during head-fixed, slow eye movements (note that the coefficient subscript *s* refers to coefficients estimated during smooth-pursuit eye movements, during which velocities were relatively slow, i.e., $<40^\circ/s$). Across our sample of neurons, the mean population VAF for Eq. 1 was 0.48 ± 0.17 for smooth-pursuit eye movements. Furthermore, we found that the same model coefficients could be used to predict the firing rate of our example neuron during the eye movements (or lack thereof) generated with passive vestibular stimulation at $0.5 \text{ Hz} \pm 40^\circ/s$ by the VOR and in VORc (Fig. 1, *C* and *D*, respectively; population mean VAF for VOR = 0.38 ± 0.22).

Prepositus Neurons Are Not Modulated by Voluntary Head Motion During Pursuit

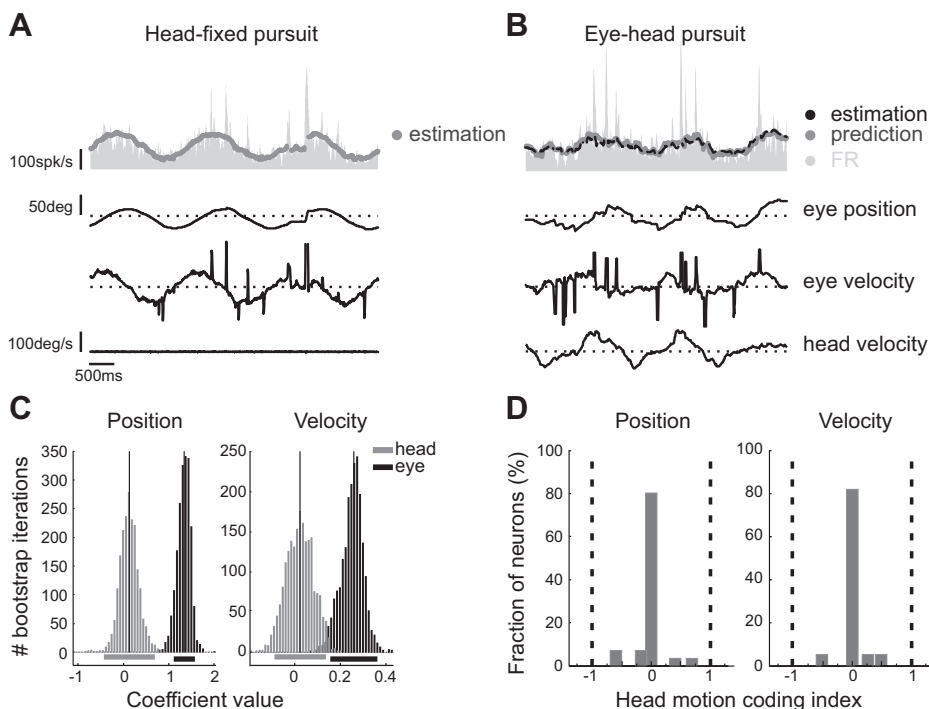
To quantify the signals encoded by prepositus neurons during voluntary head movements, we first assessed whether the same eye movement-based model, estimated during smooth pursuit (i.e., Fig. 2*A*), could be used to accurately predict a given neuron's firing rate for the voluntary head movements made during eye-head pursuit. Indeed, as illustrated for the example neuron in Fig. 2*B*, this eye-based model successfully predicted each neuron's firing rate during combined eye-head pursuit. Notably, for each neuron, the prediction by the head-restrained pursuit model was nearly as good as that of a model optimized to estimate the neuron's firing rate directly (Fig. 2*B*; population mean VAFs 0.25 ± 0.17 vs. 0.29 ± 0.15 , respectively).

Next, we directly examined the possibility that some of the variance in the firing rate of our neurons during voluntary movements encoded the actively generated head motion. To quantify the coding of head-movement information by a given neuron, we determined the best fit of a dynamic model, expanded from the first-order, eye-based model in Eq. 1 above, to include head-position and -velocity terms

$$\widehat{FR}(t) = b + k_c E(t - t_d) + r_c \dot{E}(t - t_d) + g_{pc} H(t) + g_{vc} \dot{H}(t) \quad (2)$$

where the subscript *c* refers to coefficients estimated for this "complete" model. For our population of neurons, the mean VAF provided by the complete model was 0.37 ± 0.16 . This corresponds to an average increase of only 0.08 relative to the VAF of the eye-based estimation, suggesting that neurons preferentially encoded eye, not head, motion. For each model coefficient, we obtained 95% confidence intervals using a nonparametric bootstrap approach (Carpenter and Bithell 2000).

Fig. 2. *A*: firing of example neuron OR5000 during head-fixed smooth pursuit. Dark gray trace is the firing-rate estimate based on Eq. 1. *B*: firing rate of example neuron OR5000 during active gaze pursuit. The response predicted by the smooth-pursuit estimation (dark gray trace) and firing rate estimated using Eq. 1 (dotted black trace) are superimposed on the measured firing rate. *C*: coefficient estimate distributions from 2,000 bootstrap iterations estimating the firing rate of example neuron OR5000 during gaze pursuit using Eq. 2. Black bars represent eye, and gray bars represent head position and velocity (left and right, respectively). Horizontal bars are 95% confidence intervals, and vertical black lines mark the mean of each distribution. *D*: histogram of head-motion coding index values for all prepositus neurons during gaze pursuit. Left: head/eye position; right: head/eye velocity. Dotted lines at 1 and -1 delineate boundary, where head sensitivity \geq eye sensitivity.



Briefly, we began with the original data set comprising n segments of eye-head pursuit behavior occurring between saccades and estimated the optimal eye-position (k), eye-velocity (r), head-position (g_p), and head-velocity (g_v) coefficients to describe each neuron's firing rate for this data set. We then generated 1,999 new data sets by sampling randomly with replacement from the n intersaccadic segments of the original data set. Figure 2C displays the distributions of all 2,000 estimates of each complete model coefficient for the example prepositus neuron. The distributions of the eye- and head-position coefficients (i.e., k and g_p , respectively) are compared, and the distributions of the eye velocity and head velocity (r and g_v , respectively) are compared. Notably, this example neuron was typical of our population of prepositus neurons, in that the 95% bootstrap confidence intervals for both head-related coefficients overlapped with zero. In our population, the proportion of neurons with 95% bootstrap confidence intervals overlapping zero for head-position and head-velocity coefficients was 80% and 82%, respectively. Conversely, eye-position and eye-velocity terms contributed significantly to the best estimate of prepositus neuron firing rates during active eye-head pursuit for all neurons in our population.

To further quantify the coding of head vs. eye motion by each neuron in our sample, we next calculated a "head-motion coding" index (see METHODS). Briefly, for each neuron, the ratios of head- and eye-position coefficients (g_p/k) and of head- and eye-velocity coefficients (g_v/r) were computed using the means of the bootstrap estimate distributions for each coefficient. Ratios of zero indicated eye-only encoding, whereas nonzero values indicated some head-motion sensitivity, and only indices less than -1 or greater than 1 would correspond to neurons preferentially encoding head motion. Note that in all cases, indices were between -1 and 1, indicating that neurons preferentially encoded eye motion. On average, the indices for eye-head pursuit position and velocity coefficients were not significantly different from zero ($P > 0.31$), with distributions

centered at -0.01 ± 0.24 and 0.01 ± 0.19 , respectively (Fig. 2D). Taken together, these results reveal that the same eye movement-based model can be used to predict a given neuron's firing rate during ocular-only pursuit and when voluntary head movements are made during eye-head pursuit. Thus these findings suggest that prepositus neurons predominantly encode eye- and not head-related information during the voluntary head movements produced during combined eye-head pursuit.

Prepositus Neurons Are Not Modulated by Voluntary Head Motion During Gaze Shifts

To continue our investigation of the firing properties of the burst-tonic neurons during active head movements, we next performed an analysis comparable with that detailed above to determine whether the neurons are modulated by head motion during the more rapid movements made during orienting gaze shifts. Accordingly, we first computed the optimal fit of the first-order, eye-based model in Eq. 1 to neuronal responses during saccades made when the head was restrained (i.e., head-fixed gaze shifts). Specifically, we estimated b_f , k_f , and r_f to describe the burst in each neuron's firing rate during fast, ipsilaterally directed saccades (velocity $> 300^\circ/\text{s}$; denoted by coefficient subscript f). The estimated firing rate of our example neuron is shown in Fig. 3A. For all of our recorded neurons, the mean population VAF of Eq. 1 was 0.66 ± 0.10 for saccades, indicating that it described their firing accurately.

Following this optimization, we used the same eye-based model estimated above for head-restrained saccades to predict a given neuron's firing rate during head-unrestrained, voluntary gaze shifts. The results shown for our example neuron in Fig. 3B are typical in that the same model successfully predicted its firing rate during gaze shifts in which the monkey produced voluntary head as well as eye movements (population mean VAF = 0.34 ± 0.17). Furthermore, the model's prediction was almost as accurate as a separate eye-based model,

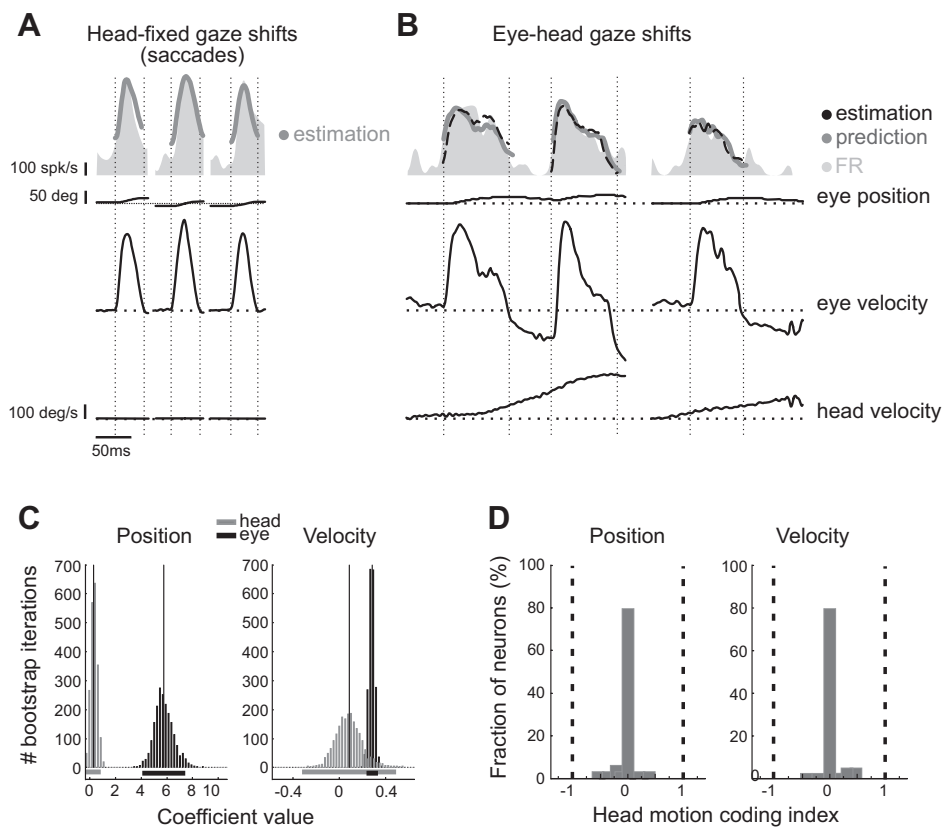


Fig. 3. *A*: activity of example neuron OR5000 during 3 ipsilaterally directed head-fixed saccades. Dark gray trace is the firing rate estimated using Eq. 1. *B*: activity of example neuron OR5000 during 3 ipsilaterally directed active eye-head gaze shifts. Firing rate predicted by coefficients estimated for head-fixed saccades (dark gray trace) and the firing-rate estimate using Eq. 1 (dotted black trace) are shown on top of the recorded response. *C*: distributions of bootstrapping results for the coefficients of Eq. 2 in estimating the firing rate of example neuron OR5000 during gaze shifts. Black bars depict eye-position and -velocity values, whereas gray bars depict head-position and -velocity values (left and right, respectively), and distribution means are marked by black lines. Horizontal bars show the span of the 95% confidence interval for each coefficient. *D*: histograms of head-motion coding indices for position and velocity coefficients (left and right, respectively) for the population of prepositus neurons during gaze shifts.

optimized to directly fit the neuron's firing rate (Fig. 3*B*; population mean VAF = 0.44 ± 0.15).

As described above for our analysis of neuronal responses during pursuit, we next addressed the possibility that sensitivity to head movements could account for additional variance in the firing rate of our prepositus neurons during active gaze shifts using a comparable nonparametric bootstrap approach. In this analysis, the new data sets were generated by randomly resampling with replacement the n saccadic segments from the original data set. Figure 3*C* illustrates the 95% bootstrap confidence intervals obtained for each of the coefficients in Eq. 2 when the complete model was applied to the example neuron's firing rate during active gaze shifts. The mean population VAF improved by only 0.07, to 0.51 ± 0.16 , again suggesting that neurons preferentially encoded eye motion. Notably, the 95% bootstrap confidence intervals of the eye-related coefficients do not include zero, whereas the 95% bootstrap confidence intervals of the head-related coefficients both span zero. This was typical of all of our recorded neurons, with 80% of the head-position coefficients and 81% of the head-velocity coefficients overlapping zero in this condition. As a result, the average head-motion coding indices for position and velocity were not significantly different from zero ($P > 0.58$; 0.02 ± 0.16 and 0.03 ± 0.17 , respectively; distributions shown in Fig. 3*D*).

Prepositus Neurons Are Not Modulated by Voluntary Head Motion Following Gaze Shifts

In addition to characterizing prepositus burst-tonic neurons during behaviors in which monkeys generated relatively slow (eye-head pursuit) and fast (gaze shifts) eye motion, we re-

corded and quantified neuronal activity during a behavior in which monkeys made eye movements with velocities in a third, intermediate range. In particular, we sought to determine whether prepositus neurons might signal the voluntary head movements generated immediately following an active eye-head gaze shift once gaze is stable. Note that for this analysis, we analyzed neural activity during contralaterally directed head movements, since they are accompanied by eye velocities in the ipsilateral direction (i.e., the neuron's "on" direction for eye motion).

First, we estimated optimal b_i , k_i , and r_i coefficients for Eq. 1 to determine the best eye-based model of prepositus firing rates during passive, whole-body rotations, which were designed to match the head trajectory of self-generated gaze shifts (see METHODS), such that peak eye velocities fall in an intermediate range (60–200°/s; denoted by subscript i). Figure 4*A* shows that this model fits well to the measured firing rate of the same example neuron that was shown above in Figs. 1–3. Across our sample of neurons, the mean population VAF for Eq. 1 was 0.36 ± 0.18 for these active-like, passive rotations.

For each neuron, we then quantified the ability of the same eye-based model to accurately predict prepositus neuronal firing rates during voluntary head movements generated immediately following contralaterally directed gaze shifts. Again, our example neuron is typical of the population in that the model that was estimated to fit its response during active-like, passive, whole-body rotations predicted its activity effectively during self-generated head motion following eye-head gaze shifts (Fig. 4*B*). Indeed, the prediction fit nearly as well as a new model optimized to directly estimate the neuron's firing rate (Fig. 4*B*). On average across all neurons, the VAFs of the

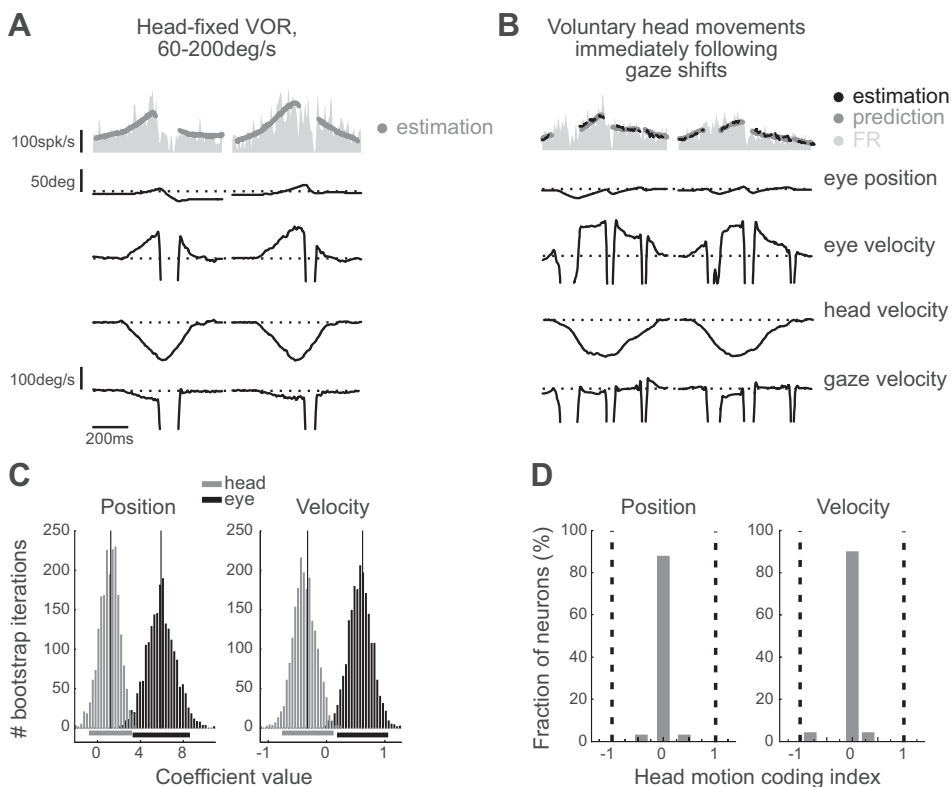


Fig. 4. *A*: response of example neuron OR5000 during VOR, generated for 2 active-like, passive, whole-body rotations in the contralateral direction. The firing-rate estimate from Eq. 1 is superimposed (gray trace). *B*: response of example neuron OR5000 during head movements generated when gaze was stable, following 2 contralaterally directed gaze shifts. The predicted firing rate based on the passive VOR estimate (gray trace) and the firing rate estimated using Eq. 1 (dotted black trace) are superimposed on the measured firing rate. *C*: distributions of coefficients for Eq. 2 estimate of the firing shown in *B*. Horizontal black and gray bars depict 95% confidence intervals for eye and head coefficients, respectively, and the mean of distribution is marked by black lines. *D*: histograms of head-motion coding indices of all prepositus neurons recorded in this condition.

prediction and the estimate were 0.20 ± 0.13 vs. 0.27 ± 0.16 , respectively.

Finally, we determined whether additional variance could be accounted for by head-motion sensitivity in our population of prepositus neurons during large, voluntary head movements involving intermediate-velocity eye movements. Based on the same analysis used above for pursuit (Fig. 2C) and gaze shifts (Fig. 3C), we obtained 95% bootstrap confidence intervals (Fig. 4C) for each of the coefficients in Eq. 2. The mean population VAF for the complete model was 0.33 ± 0.18 , corresponding to an average increase of only 0.06, with the addition of head motion-related terms and suggesting predominantly eye-related signaling. Notably, for our example neuron, both of the 95% bootstrap confidence intervals for the head-related coefficients (Fig. 4C) spanned zero, and similarly, across our recorded population, 88% and 90% of head-position and head-velocity coefficient 95% bootstrap confidence intervals, overlapped zero, respectively. In contrast, the example neuron's 95% bootstrap confidence intervals for eye-position and eye-velocity coefficient estimates (Fig. 4C) did not include zero. This was typical of all recorded neurons. Notably, for our population of prepositus neurons during voluntary head movements following gaze shifts, the distributions of head-motion coding indices calculated for position and velocity coefficients were centered at -0.0008 ± 0.12 and -0.03 ± 0.22 , respectively, and were not significantly different from zero ($P > 0.28$; Fig. 4D).

Prepositus Neurons Encode Eye-Related Signals, Similarly to Abducens Motoneurons

Taken together, the results so far indicate that burst-tonic neurons in the nucleus prepositus predominantly encode eye movements throughout head-fixed, passive, and active condi-

tions involving a full range of eye-motion velocities. Interestingly, these results are comparable with those obtained for abducens motoneurons during head-unrestrained behaviors (Sylvestre et al. 2001). Indeed, the eye-based model (Eq. 1) used in this study has been used previously to characterize abducens motoneurons (Sylvestre and Cullen 1999). Accordingly, we, in turn, applied our complete model (Eq. 2) to a population of 39 abducens motoneurons to compare the above results with those for neurons known not to carry head-motion signals.

Figure 5 summarizes our results obtained for abducens motoneurons, showing neuronal responses during behaviors characterized by relatively slow and fast eye-velocity ranges (i.e., pursuit and gaze shifts) as examples. First, we quantified the ability of the eye-based model (Eq. 1) to describe the firing rate of each neuron during head-fixed smooth pursuit (example neuron shown in Fig. 5A; mean population VAF = 0.65 ± 0.21). We subsequently used the model coefficients optimized in this head-fixed condition to predict the firing rate of each neuron during combined eye-head pursuit (Fig. 5A). Across all abducens motoneurons, predicted firing rates matched firing-rate estimates properly for the same model structure when the coefficients were optimized directly for the eye-head pursuit condition (Fig. 5A; mean population VAFs for prediction and estimation were 0.31 ± 0.30 and 0.41 ± 0.22 , respectively). Finally, we applied the complete model (Eq. 2) to the firing rate of each neuron during eye-head pursuit to confirm that responses to head motion do not contribute to their firing. Indeed, the mean population VAF for Eq. 2 was 0.48 ± 0.23 , a change of just 0.07 relative to Eq. 1. Figure 5A depicts bootstrapped coefficient estimates for our example abducens motoneuron. The 95% bootstrap confidence intervals for eye position and eye velocity show that the neuron had significant eye-motion sensitivity, whereas the 95% bootstrap confidence intervals for

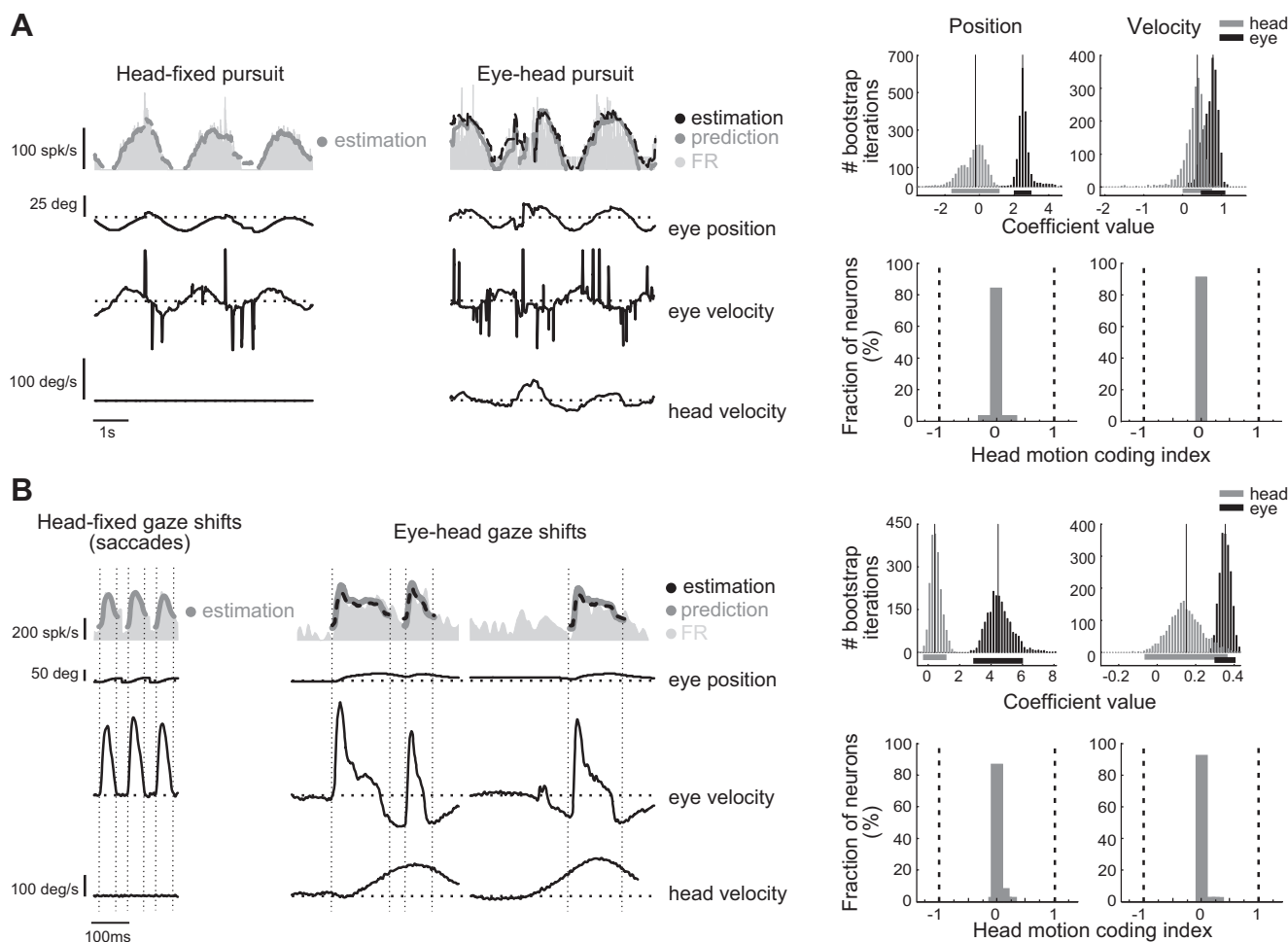


Fig. 5. Results of analysis done on example abducens motoneuron OR4401 in the slow and fast eye-velocity conditions. *A*: responses during head-fixed pursuit and gaze pursuit estimated and predicted, respectively, with Eq. 1 (dark gray traces, left); 95% bootstrap confidence intervals estimated from gaze-pursuit firing rate fit with Eq. 2 (right, top); and summary plots of head-motion coding indices for all abducens motoneurons in the active gaze-pursuit condition (right, bottom). *B*: activity of the same neuron during head-fixed saccades and gaze shifts, with Eq. 1-estimated and -predicted firing rates, respectively (dark gray traces, left); distributions of Eq. 2 coefficient estimates for the example neuron during gaze shifts (right, top); and head-motion coding index distributions for the entire population of abducens motoneurons during gaze shifts (right, bottom).

head-motion coefficients overlapped zero. Notably, as expected, we obtained these results for the majority of neurons in our population of motoneurons (the 95% bootstrap confidence intervals of 84% of head-position and 91% of head-velocity coefficient estimates overlapped zero), leading to head-motion coding indices averaging 0.004 ± 0.098 and 0 ± 0 , respectively, which were not significant ($P > 0.84$; Fig. 5A).

We similarly analyzed our population of abducens motoneurons during head-fixed saccades and gaze shifts. Figure 5B shows the example neuron's responses in these two behavioral conditions. Each neuron's firing rate during saccades was estimated successfully by optimizing the eye-based model described in Eq. 1 (mean population VAF = 0.70 ± 0.098); similarly, this same model accurately predicted a given neuron's firing rate during gaze shifts (mean population VAF = 0.34 ± 0.28 ; Fig. 5B). Notably, in the latter case, our predictions based on each neuron's firing rate during head-fixed saccades were nearly as accurate as estimates obtained using Eq. 1 to directly estimate the same neurons' firing rates during gaze shifts (example neuron: Fig. 5B; mean population VAF = 0.45 ± 0.15).

To demonstrate a lack of response to head-motion coding by abducens motoneurons during gaze shifts, we again used Eq. 2 to obtain estimates of head- as well as eye-position and -velocity sensitivities (mean population VAF for Eq. 2 = 0.49 ± 0.16). Notably, this was an average increase in VAF of 0.04 across all neurons, corresponding to the fact that neurons encode eye-rather than head-related information. In agreement with this, the 95% bootstrap confidence intervals of the estimates of head-position and head-velocity coefficients overlapped zero for 87% and 92% of our sample, respectively. Moreover, the distributions of head-motion coding indices for all of our samples of abducens motoneurons were centered at 0.02 ± 0.06 and 0.02 ± 0.08 , respectively, and were not significantly different from zero ($P > 0.11$) for gaze shifts.

Finally, to complete our study and allow a direct comparison with our analysis of prepositus burst-tonic neurons, we also compared the responses of abducens motoneurons during active-like, passive, whole-body rotations with those during the period in which voluntary head movements are made immediately after gaze shifts (i.e., comparable with Fig. 4). For each neuron, we again estimated the coefficients for the eye-based

model (Eq. 1) in the passive and active conditions. We then determined whether adding head-related terms [i.e., complete model (Eq. 2)] improved our ability to fit each neuron's firing rate during active head movements. Similar to the results of our analysis of these neurons during pursuit and gaze shifts, we found that the 95% bootstrap confidence intervals obtained for the added head-position and head-velocity terms resulted in head-motion coding indices that were not significantly different from zero for 82% and 90% of our sample, respectively.

DISCUSSION

The results of this study demonstrate that burst-tonic neurons, which are typical of the primate nucleus prepositus, do not signal head-related information during the voluntary head motion made in eye-head pursuit and gaze shifts, as well as that produced when gaze is stable, immediately following gaze shifts. Notably, during these active head-movement behaviors, neurons encoded eye-motion signals in the same manner as during head-restrained, passive paradigms (e.g., spontaneous eye movements, smooth pursuit, saccades, and VOR). In particular, the same first-order model characterized by bias, eye-position, and eye-velocity terms, which described a given neuron's firing rate in passive conditions, effectively predicted its firing rate in the corresponding active condition. We conclude that burst-tonic neurons in the primate nucleus prepositus act in a manner similar to abducens motoneurons across behavioral conditions and thus do not convey a head-motion signal to the head-direction cell pathway during voluntary head movements.

Nucleus Prepositus and the Encoding of Eye vs. Head Motion

The nucleus prepositus is thought to contribute to spatial perception as a relay of vestibular signals to the head-direction

pathway [Brown et al. (2005); reviewed in Taube (2007)]. Specifically, in the same way that the nucleus prepositus is known to be an essential component of the neural integrator that generates eye-position signals for the VOR and saccades (Cannon and Robinson 1987), studies in rats (Bassett and Taube 2001) led to the proposal that the nucleus prepositus might transform vestibular responses into head-position signals to update heading perception. Here, we have shown, however, that burst-tonic neurons, which constitute the majority of prepositus neurons, do not encode a head-motion signal during voluntary movements in monkeys. Rather, we showed that in agreement with previous studies of neuronal responses during head-fixed eye movements (McFarland and Fuchs 1992; Sylvestre et al. 2003) and passive head movements (Cullen et al. 1993; McCrea and Cullen 1992), these neurons predominantly encode eye-related signals.

Specifically, we found that an eye-based, first-order linear model of neuronal firing rates could accurately predict prepositus responses during voluntary head movements. Notably, model parameters estimated in three head-restrained conditions, characterized by different velocity ranges, provided good fits to firing rates recorded during active head-movement behaviors that involved comparable eye motion. Thus our finding that a first-order, eye-based model (i.e., including eye-position and -velocity terms; Eq. 1) described prepositus neuron firing rates well during voluntary head movements is similar to the results found previously for extraocular motoneurons (Sylvestre et al. 2001), as well as for prepositus burst-tonic neurons during head-fixed saccades (Sylvestre et al. 2003). Figure 6 superimposes Eq. 1 coefficients optimized for each of our head-fixed and passive conditions and those optimized for the corresponding active conditions for both our prepositus burst-tonic and abducens neurons. Notably, comparable coefficients were typically obtained across behavioral conditions. Import-

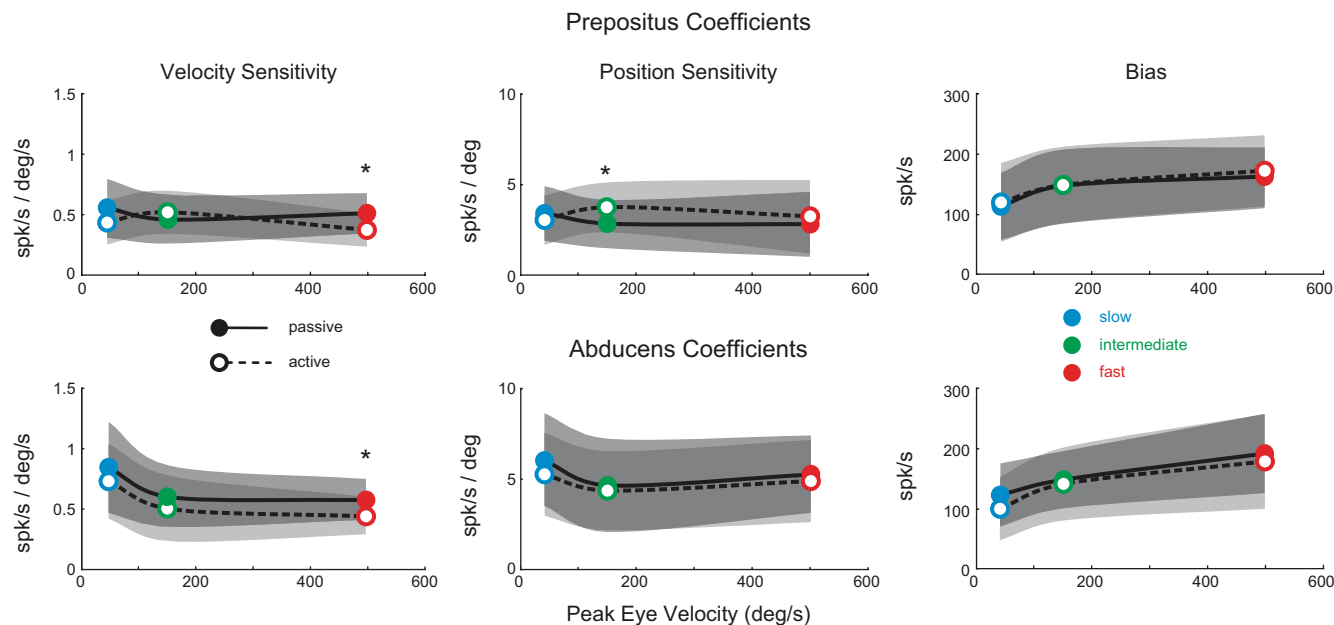


Fig. 6. Estimated eye-velocity coefficients, eye-position coefficients, and biases for the eye-based model of firing rate (Eq. 1), plotted as a function of eye velocity (blue, green, and red points correspond to the slow, intermediate, and fast paradigms, respectively). Values shown are means across all recorded prepositus (top) and abducens (bottom) neurons; shading denotes SD. Comparable estimates (darkest shading) were obtained for neurons in head-restrained (filled symbols, solid lines) and active (open symbols, dotted lines) conditions (* $P < 0.05$, coefficients that were different by paired t -test), and trends were largely similar between prepositus neurons and abducens motoneurons.

tantly, the coefficient estimates in our eye-based models for prepositus burst-tonic neurons exhibited similar trends as a function of eye velocity to those reported previously for motoneurons (Sylvestre and Cullen 1999): whereas bias estimates increased with increasing eye velocity, estimated eye-position and eye-velocity sensitivities decreased with increasing eye velocity.

This result provides further insight into the role of the primate nucleus prepositus. For example, as is the case for motoneurons, the output of burst-tonic neurons in the nucleus prepositus is modulated more strongly (i.e., displays higher eye-motion sensitivities) to produce smooth-pursuit movements than saccadic eye movements. Sylvestre and Cullen (1999) concluded from this behavior in motoneurons that abducens drives the oculomotor plant more efficiently during saccades when antagonist motoneurons are known to be pausing than during smooth pursuit when antagonist motoneurons are simultaneously firing. Because models of burst-tonic prepositus neurons reveal equivalent trends across eye velocities, it is possible to consider that prepositus signals also correspond directly to the motor command being sent to the eye. By this logic, the nucleus prepositus should not encode any head motion-related signals. Such a proposal is consistent with the findings of Green et al. (2007), which suggested that the nucleus prepositus plays a primary role in premotor circuitry and effectively encodes a copy of the eye-motor command itself.

Having established that an eye-based model effectively describes the output of the majority of neurons in the nucleus prepositus, we applied additional analyses to explicitly test for head-motion sensitivities in the same population during active movements. With the use of an extended model structure, which included head-position and -velocity terms (Eq. 2), we confirmed that estimates of head movement-related coefficients were not significantly different from zero for our population. Importantly, we obtained comparable results when we applied the same analysis with our population of abducens motoneurons, which robustly encode eye-movement signals during all behavioral conditions (Cullen et al. 1993; Sylvestre and Cullen 1999; Sylvestre et al. 2001). Note that for the few neurons in each population, for which we obtained nonzero head motion-related coefficient estimates, the magnitudes of their coefficients were consistently smaller than those of the corresponding eye movement-related coefficient estimates (see head-motion coding index results). Thus overall, our results suggest that the firing rates of prepositus burst-tonic neurons do not encode substantive vestibular information during active head movements.

Functional Implications of Eye-Only Encoding by Prepositus Neurons

In the present study, we have established that burst-tonic neurons in the primate nucleus prepositus predominantly encode eye movements, even during active head motion. Our findings are consistent with previous studies in primates that have recorded both eye motion and firing rates during head-fixed eye movements and passive head-motion paradigms. Specifically, most neurons in the nucleus prepositus (~80%) can be characterized as burst-tonic neurons, which encode eye but not head-movement information (Cullen et al. 1993; Mc-

Farland and Fuchs 1992; Sylvestre et al. 2003). Here, we show further that these same burst-tonic neurons continue to encode eye rather than head motion during voluntary head movements. This is not surprising when considering the afferent projections to prepositus. Inputs to the nucleus prepositus are nearly identical to those received by abducens [reviewed in McCrea and Horn (2006)], which is in agreement with our comparable results for prepositus burst-tonic neurons and abducens motoneurons. Furthermore, our results, which demonstrate that the majority of nucleus prepositus neurons encodes only eye-position and -velocity signals throughout head-fixed, passive, and active eye and head movements, are more consistent with the proposed roles of the nucleus prepositus in gaze control and gaze stabilization (Belknap and McCrea 1988; McCrea and Baker 1985).

Indeed, studies in cat and goldfish suggest that neurons in the nucleus prepositus predominantly encode eye-related information across a wide range of species [cat: Delgado-Garcia et al. (1989), Escudero et al. (1996), Hardy and Corvisier (1996), Lopez-Barneo et al. (1982); goldfish: Aksay et al. (2000), Debowy and Baker (2011)]. Additionally, although recordings have not yet been made in the rat nucleus prepositus with simultaneous measurement of eye movements, early work by Lannou et al. (1984) reported that responses of neurons exhibited increased firing during contralateral head rotations (corresponding to ipsilateral eye rotations during VOR) and produced bursts of activity with ipsilateral on directions during quick phases of nystagmus. Both observations are consistent with the burst-tonic characteristics known in the nucleus prepositus of cats and monkeys, and so, it is likely that prepositus neurons signal eye motion in rats as well.

Given that prepositus neurons robustly encode eye-movement information during active and passive movements, the question arises: what function does this information serve with respect to its known projections? The coding of eye movement is consistent with the known projections from the nucleus prepositus to oculomotor and gaze-control structures [monkey: Hartwich-Young et al. (1990), Robinson et al. (1994); cat: Belknap and McCrea (1988), Escudero et al. (1992), Langer et al. (1986), McCrea and Baker (1985); rat: Iwasaki et al. (1999), Ohtsuki et al. (1992); guinea pig: Corvisier and Hardy (1991)]. However, this property is more difficult to reconcile with the nucleus prepositus' known ascending projections to regions such as the dorsal tegmental nucleus. In rat, the dorsal tegmental nucleus has been shown to receive projections from the nucleus prepositus and send signals to the LMN, which contain head-direction cells (Brown et al. 2005). Whereas an analogous, ascending projection has yet to be demonstrated in monkeys, it is likely to exist, given that similar connections have also been reported in cat (Gerlach and Thier 1995; Higo et al. 1990). Accordingly, taking together the known anatomical connections from the nucleus prepositus to the head-direction circuitry and its eye movement-related activity, an important question remains: what is the significance of an eye-movement signal in the head-direction pathway?

Interestingly, Robertson et al. (1999) suggested that primate head-direction cells might exhibit tuning to gaze angle as well as heading. We suggest that head-direction cells might also code eye (gaze)-related signals in species with relatively smaller oculomotor ranges [e.g., cats: Guitton et al. (1984); rats: Fuller (1985)] but that these signals would be less obvious

because eye movements constitute only a small component of orienting behavior in these species. Notably, these eye motion-related signals may play a role in mediating tuning of the upstream spatial perception circuitry, as suggested by a recent study on grid cells in primates (Killian et al. 2012).

It is important to note that 20% of neurons in the monkey nucleus prepositus are characterized by sensitivities to head as well as eye motion (Cullen et al. 1993; McFarland and Fuchs 1992). Notably, this subpopulation of neurons, termed eye-head velocity neurons, not only encodes eye position and velocity (like burst-tonic neurons) during head-restrained eye movements but also robustly encodes head motion throughout VORc during passive rotations (with the preferred direction of head velocity toward the same side as that of pursuit eye motion). Accordingly, these firing behaviors are consistent with the nucleus prepositus' long-appreciated role in premotor control of pursuit eye movement. Moreover, during voluntary head movements (e.g., gaze pursuit and eye-head gaze shifts), eye-head velocity neurons continue to encode both eye and head motion. More specifically, their firing rates have been found to encode eye as well as head motion with the same sensitivities as during head-restrained eye movements and passive rotations (Roy and Cullen 2003). Taken together, it is clear that even with some head-related output, all neurons in the nucleus prepositus encode robust eye-movement information. Accordingly, we assert that the nucleus prepositus functions to stabilize gaze, not to signal heading, and we expect that future electrophysiological studies will demonstrate that another brain area relays vestibular signals to the head-direction pathway.

For example, the results of lesion and inactivation studies [reviewed in Taube (2007)] suggest that signals from the vestibular labyrinth are necessary for head-direction cell tuning. Anatomical studies further suggest that aside from the nucleus prepositus, two additional nuclei might play a role in relaying vestibular signals to the head-direction pathway: the supragenual nucleus and the paragigantocellular nucleus [Biazoli et al. (2006); Cornwall et al. (1990); Liu et al. (1984); reviewed in Shinder and Taube (2010)]. Given that the nucleus prepositus predominantly encodes eye-movement information during active and passive motion, we speculate that neurons in one or both of these areas may encode head-related information more robustly. Whereas future investigations are needed to confirm this proposal, the report that lesions of the supragenual nucleus in rats produce instability in head-direction cell tuning (Clark et al. 2012) is consistent with this idea.

Conclusion

In summary, our results confirm that neurons in the primate nucleus prepositus encode the relevant signals to play a role in premotor control of gaze, as well as gaze stabilization. We have demonstrated that this role extends beyond that suggested by the existing body of literature that had implicated prepositus in eye-movement signaling during head-fixed and passive conditions. Importantly, here, we show that burst-tonic neurons, which constitute the majority of neurons in the nucleus prepositus, encode eye position and eye velocity but not head position or head velocity during a wide range of voluntary head-movement behaviors. Moreover, since it is well situated to contribute to spatial perception, we speculate that the eye-

movement information encoded by the nucleus prepositus may shape the spatial tuning of neurons in the head-direction and (potentially) grid-cell networks.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.D. and K.E.C. conception and design of research; A.D. and K.E.C. performed experiments; A.D. and K.E.C. analyzed data; A.D. and K.E.C. interpreted results of experiments; A.D. and K.E.C. prepared figures; A.D. and K.E.C. drafted manuscript; A.D. and K.E.C. edited and revised manuscript; A.D. and K.E.C. approved final version of manuscript.

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