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THE NEURAL INTEGRATORS OF THE MAMMALIAN SACCADIC SYSTEM

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1. ABSTRACT

The neural velocity to position integrators transform the saccade related signal of the burst generators into an eye position related tonic signal they convey to motoneurons. They are largely confined to three heavily interconnected midbrain structures: 1) The interstitial nucleus of Cajal (NIC), 2) The nucleus prepositus hypoglossi (NPH), 3) The vestibular nuclei (VN). Integration in the horizontal and vertical planes is accomplished largely independently by the NPH-VN and the NIC-VN complexes, respectively. Cells in these regions carry a more or less intense phasic signal related to saccades and a tonic signal related to eye position. Depending on the relationship between the rate of their discharge and the position of the eyes, these cells have been further subdivided into regular or irregular, more or less sensitive, and bi-directionally or uni-directionally modulated. The present review provides a brief description of their discharge pattern and that of burst neurons and extraocular motoneurons. Then, evidence concerning the input-output connections of relevant cell classes is summarized. Finally, several modelling attempts to simulate the neural velocity-to-position integrators are presented and their verisimilitude is evaluated in the light of psychophysical, anatomical, physiological and neurological evidence.

2. INTRODUCTION

The behavioral repertoire of humans and other animals contains a large variety of ocular movements (convergent, divergent, saccadic, nystagmic slow phases and smooth pursuit). The best understood of the relatively independent neural circuits that control them is the one generating saccades (reviewed in ref. 1). These are ubiquitous movements that primates execute at a rate of about 3 per second to rapidly reorient their line of sight towards salient features of the surrounding world. Figure 1 is a schematic overview of the neural machinery that controls saccades. The top part of this figure is devoted to higher order structures such as the superior colliculus (SC) the cortical eye fields (Cx), the thalamus and the basal ganglia (Str/STh/Th/SNR) and the cerebellum (Cb); these structures evaluate the saliency, importance and context of image features and issue commands for the execution of saccades of appropriate direction and amplitude. The command signals are conveyed to the burst generators which determine the metrical and dynamical properties of saccades. The horizontal and vertical size of saccades is separately determined by the horizontal (HBG) and vertical (VBG) burst generators. The former is located in the caudal paramedian pontine reticular formation (PPRF; 2, 3, 4) while the latter occupies the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF; 5, 6, 7, 8). Each burst generator distributes its output to extraocular motoneurons in such a way as to account for eye conjugacy (9), and to other burst generators in such a way as to ensure the push-pull coupling of burst generators with opposite on-directions and the two-dimensional coordination of burst generators with orthogonal on-directions.

The output of the saccadic system is carried by extraocular motoneurons (the HMN and VMN blocks of figure 1). These emit a burst of discharge that is proportional to the size of saccades in their preferred direction (left or right, up or down) and then settle into a tonic discharge that is proportional to eye position along

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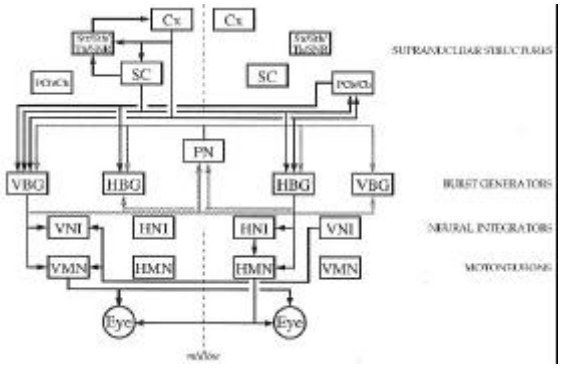

Figure 1. Organization of the mammalian system that controls rapid eye movements. Motoneurons (MN), integrators (NI) and burst generators (BG) are illustrated in a bi-directional (left-right), two-dimensional (horizontal-vertical) arrangement. Burst generators of different directions are coupled via the OPN feedback loop. Trans-cortical, trans-collicular and trans-cerebellar loops and their connections to the burst generators occupy the top part of the figure. Stippled lines indicate inhibitory connections. All other connections are excitatory. Abbreviations: Cx, cortex; HBG, horizontal burst generators; HMN, horizontal motoneurons; HNI, horizontal neural integrators; PCb/Cb, precerebellar neurons and cerebellar circuits; PN, pause neurons; SC, superior colliculus; Str/Sth/Th/SNR, striatal, subthalamic, thalamic and nigral (of the pars reticulata) units; VBG, vertical burst generators; VMN, vertical motoneurons; VNI, vertical neural integrators.

the same direction (10). Much of the phasic presaccadic signal is conveyed to them by the burst generators, directly. The tonic eye position signal is extracted from the phasic with the help of a process akin to mathematical integration (the HNI and VNI blocks of figure 1). This review summarizes evidence concerning the neural implementation of this process. Section 3, provides a brief description of the areas that are thought to house the neural integrators and the symptoms that emerge when they are lesioned. Evidence concerning the morphological and physiological properties of the neurons that comprise the integrators is summarized in Section 4. Then, evidence concerning the source of their input (Sections 5.1 and 5.2) and the targets of their output (Sections 5.3 and 5.4) signals is reviewed. Finally, modelling efforts to explain how a piece of neural tissue can engage in calculus are evaluated in Section 6.

3. REGIONS

As with burst generation, several cell assemblies are needed to implement neural integration in different planes. Integration in the vertical plane is compromised following insults to the interstitial nucleus of Cajal (NIC). This is the largest of the cell groups that lie loosely along the path of the medial longitudinal fasciculus (MLF); it was described in 1911 by Cajal (11) whose name it bears. The NIC borders with the nucleus of Darkschewitsch, the periaqueductal gray (PAG) the nucleus Edinger-Westphal and the oculomotor nucleus, borders that are easily defined on cytoarchitectonic grounds (12). Other borders, i.e., with the reticular formation, laterally and dorsally, and the rostral interstitial nucleus of the MLF, rostrally, are more difficult to discern. Two distinct cell classes have been recognized within the NIC, with the help of the Golgi-Kopsch method: one of large pyramidal or multipolar neurons and the other of small to medium size pyramidal, fusiform or round cells (13).

Symptoms due to lesions of the velocity to position integrators depend on the oculomotor subsystem examined. In the case of the saccadic system, they consist in gaze nystagmus (i.e., inability to hold the eyes at eccentric positions; 14), which is vertical after NIC lesions. In the cat, bilateral electrolytic lesions of the NIC cause postsaccadic drift of the eyes with a time constant as low as 150 ms (average: 0.77 s; range: 0.15 - 1.74 s; 15, 16). Bigger lesions extending into the neighboring reticular formation can further reduce the average time constant of the postsaccadic drift (to 390 ms; 16) but not to the mechanical time constant of the feline oculomotor plant (60 ms; 17). Due to the multitude of fibers that traverse the NIC results obtained with electrolytic lesions are difficult to interpret. To avoid the damage of perforant fibers, feline NIC neurons were chemically lesioned either permanently following the injection of an excitotoxin (kainic acid), or reversibly following the infusion of a GABA agonist (muscimol). Both have been shown to generate postsaccadic eye drifts with a time constant equal to about 0.4 s (0.38 s, ref. 18; 0.39 ± 0.14 s, ref. 19). Clearly, velocity to position integration can not take place in the vertical saccadic system of the cat without the participation of NIC cells.

Similarly, unilateral inactivation of the NIC with the help of muscimol prevents monkeys from holding eccentric vertical eye positions, without affecting their ability to hold eccentric horizontal eye positions (20). Here, an almost total failure of the vertical integrator is indicated by the fact that the eyes drift post-saccadically with a time constant of only about 100 - 400 ms. The same is true of human patients with midbrain lesions involving the NIC who also display vertical (but not horizontal) gaze holding failure (21, 22).

Given the fact that the vertical extraocular muscles cause the eyes to roll as well as move vertically, it is hardly surprising that NIC lesions cause the eyes to drift around the torsion axis with a time constant that can also be as low as 100 - 200 ms (20). However the vertical deficit and the torsion deficit are not alike. The former restricts the range of eye positions that can be reached after a saccade more or less severely depending on the size of the lesion. In contrast, the torsion deficit introduces an eye roll in either a clockwise (right lesion) or a counterclockwise (left lesion) direction (20, 23). Accordingly, nullifying a torsion bias could be one of the normal jobs of the NIC.

Although necessary, it is doubtful that the NIC suffices for velocity to position integration in the vertical plane. The participation of secondary vestibular neurons is indicated by the fact that bilateral MLF lesions cause vertical gaze nystagmus in the monkey (24). Similar nystagmus afflicts human patients who suffer from bilateral internuclear ophthalmoplegia (25). Similarly, cats are unable to maintain eccentric eye position (the time constant of the drift that follows vertical saccades can be as low as 0.7 s) when bilateral parasagittal cuts of the brainstem lateral to the MLF disconnect the vestibular from the oculomotor nuclei (26). The

contribution of secondary vestibular neurons to integration in the vertical saccadic system is discussed in Sections 4.3, 5.5 and 5.6.

Integration in the horizontal saccadic system is compromised by lesions of the nucleus prepositus hypoglossi (NPH). This nucleus lines the floor of the fourth ventricle from the midline to the medial vestibular nucleus laterally and from the abducens nucleus rostrally to the hypoglossal nucleus caudally. It contains a morphologically heterogeneous population of neurons which will be described in Section 4.2. Electrolytic lesions of the NPH have been shown to cause horizontal gaze nystagmus in both the cat (27) and the monkey (28). To avoid the interpretative difficulties accompanying the perforant path problem, the NPH has also been lesioned with injections of kainic acid in both the cat (29) and the monkey (30). The ensuing postsaccadic drift was bilateral and its time constant could be as low as 200 ms whether the injection was unilateral or bilateral injection. Vertical eye movements were also affected but not as severely (the time constant of the vertical post-saccadic drift was equal to 2.5 s; ref. 30). More recently, small, permanent lesions of a subregion of the NPH (the marginal zone) following ibotenic acid injections were shown to produce gaze holding failure ipsilateral to the injection and the appearance of horizontal drifts with a time constant smaller than 300 ms (31, 32, 33).

A second oculomotor subsystem, the one that subserves the vestibuloocular reflex (VOR), also needs a velocity to position integrator to function properly. The reason is that the input to the system (firing rate of primary vestibular afferents) is proportional to (and in phase with) the angular velocity of the head (34) whereas the output of the system (motoneuron discharge) is proportional to (and in phase with) eye position (35). Furthermore, the phase difference between head velocity and eye velocity is equal to 180 deg for frequencies ranging between 0.08 and 6.45 Hz (36). The problem is not serious for high frequencies (above about 1 Hz) of head rotation (cf. figure 3 of ref. 37). In part, this is due to the fact that signals carried by vestibulo-oculomotor fibers reflect head velocity better than those carried by average primary afferent fibers (38, 39). Also, orbital mechanics endow the eyes with low-pass filtering properties (40). The necessity for an integration step in the vestibular system becomes increasingly evident as the frequency of stimulation decreases. The response properties of vestibular neurons and their implications for integration in the oculomotor system are discussed in Sections 4.3 and 5.5.

Constant velocity rotation in the dark produces a sequence of saccadic and slow eye movements (nystagmus). When the rotation stops an after-nystagmus develops in the opposite direction. The time constant of the development and the decay of the slow phase nystagmic velocity is equal to about 20 s. This value is considerably longer than the time constant of the cupula (about 6 s; ref. 34), a prolongation due to the presence of a velocity storage integrator. The velocity storage integrator is also employed in a third oculomotor subsystem, the one that subserves the optokinetic nystagmus (OKN). Rotation of a drum around the animal at constant velocity, leads to an increase of eye velocity to a plateau that matches the velocity of the drum (OKN); eye velocity slowly drops to zero after the lights are turned off (optokinetic after-nystagmus, OKAN). Both OKN and OKAN are due in part to the charging and discharging of the velocity storage integrator.

There is evidence to indicate that the NIC and the NPH are needed for these additional oculomotor integrators to function properly. Lesions of the NIC cause phase advancement of the vertical vestibulo-ocular responses in the cat. At head rotation frequencies of about 0.1 Hz, the phase advancement of the vertical VOR can be as big as 80 deg and its gain is reduced while the horizontal VOR is normal (15). Although present in unilateral lesions, this effect is more pronounced when the lesion is bilateral (26). Humans with midbrain lesions involving the NIC display impaired pitch VOR (i.e., gain reduction and phase advancement; 21, 22). Similarly, electrolytic NPH lesions in cats reduce the gain of the VOR by a lot (in particular for small frequencies of stimulation), shift its phase from eye position to eye velocity and destroy the OKN (27); these results have been replicated with kainic acid injections in the MVN and the NPH of the cat (29). Kainic or ibotenic acid injections in the MVN and the NPH of the monkey evoke a step change of eye position in response to a step change in the velocity of vestibular or optokinetic stimulation (indicative of integrator failure; 30) as well as changes in the build-up and decay of the vestibular and optokinetic nystagmus (the time constant of velocity storage decreased to about 5 s in the former and 3.5 s in the latter), albeit transiently. More recently, permanent lesions of the NPH were shown to abolish the OKN and VOR toward the side of the lesion (33). The need to preserve the integrity of commissural fibers is indicated by the fact that midline medullary section of fibers crossing caudal to the abducens nucleus causes velocity storage deficits, abolishing OKAN and shortening the time constant of the VOR (41).

This evidence should not be interpreted to indicate that the velocity to position and the velocity storage integrators reside in the same brain areas. There is considerable evidence to suggest that the opposite might be true. Firstly, certain brain stem lesions can reduce the time constant of post saccadic drifts to less than 2 s while the time constant of vestibular or optokinetic post-rotatory nystagmus remains high (more than 16 s; ref. 30). Whereas large lesions of the NPH can destroy the OKN and the VOR toward the side of the lesion (33) smaller lesions prolong (instead of shortening) the vestibular per- and post-rotatory response to steps of velocity and the charging stage of the OKN but do not affect the OKAN (32). Furthermore, small unilateral injections of kainic acid (42) or muscimol (43) in the cat, have been shown to produce bilateral horizontal (but not vertical) gaze holding failure when confined to the NPH or the central MVN and horizontal contraversive nystagmus in the dark when confined to the rostral MVN. The MVN injection did not compromise gaze holding and neither the NPH nor the MVN injection interfered with OKN and OKAN. Also, electrical stimulation of the NPH and the vestibular nuclei has been shown to evoke distinct eye movements. Slow ipsiversive ones are evoked from the NPH and

Table 1. Relationship between the discharge of NIC neurons and parameters of ocular movement

Cell Type		species	N	k (spikes/s/deg)	F_0 (spikes/s)	CV	r (spikes/s/deg/s)	fi (deg)	Ref
BT	(mean ± SD)	cat	41	3.9±1.2	75		0.15	50	55
	(range)			1.5 - 6.7	35 - 133	0.04 - 0.29		5 - 100	
Pitch	(mean ± SD)	cat	44		34	0.61		59	55
	(range)			3 - 4 (n = 12)	3 - 91	0.15 - 1.7		5 - 155	
BT	(mean ± SD)	monkey	38	2.6	79		0.44	37.9±11	54
	(range)			0.6-9				24-62	
IrT	(mean ± SD)	monkey	26	2.0±1.5				42.0±15.6	54
	(range)			0.5 - 7.7				17 - 75	

Abbreviations. a: Computed from saccades (peak rate vs. peak velocity); b: Computed from smooth pursuit; c: Computed from vestibular slow phases; k: slope of the rate-position curve; F_0: Discharge at primary position; CV: coefficient of variation; r: slope of the rate-velocity curve; fi: phase difference between discharge and eye position; BT: Burst-tonic neurons; IrT: irregular tonic neurons.

nystagmus with gradual onset and offset (i.e., the time constant of the make and the break of the nystagmus was similar to the time constant of OKN and OKAN) from vestibular nuclear regions (44). Apparently, the regions that evoke nystagmus contain vestibular only cells (45); despite some quantitative differences, similar nystagmus is evoked in response to stimulation of the vestibular nerve. Probably the most convincing evidence to date concerning a separation of the velocity to position and the velocity storage integrators has been obtained in the goldfish by Pastor and his colleagues (46). A hind brain nucleus (nucleus I) of this species has been found to contain neurons firing in relation to eye position whether the eye movement is spontaneous or due to sinusoidal head rotation. Its bilateral inactivation following lidocaine injections was shown to produce binocular horizontal postsaccadic drifts with a time constant as low as 0.3 s, and severe reduction of the gain (by 80%) and phase advancement of the VOR (by 70 deg at 0.25 Hz). A different nucleus (nucleus II) has been shown to contain cells which discharge in relation to eye velocity during sinusoidal head rotation. It is inactivation of this second nucleus (again with lidocaine injections) which has been shown to abolish the velocity storage integrator of the vestibular system (dramatically reducing the VOR time constant to a value much lower than the cupular one) without interfering while the horizontal velocity to position integrator.

All in all, this evidence suggests that the NIC and the NPH together with vestibular nuclei are largely responsible for velocity to position integration in the vertical and horizontal saccadic systems. It is less clear that these structures participate in velocity storage in the vestibular and optokinetic systems or that they suffice for all velocity to position integration in the oculomotor system. Participation of the cerebellum has been suggested because its destruction reduces the time constant of postsaccadic drifts (both vertical and horizontal) to about 1.3 s (47, 48, 49) and advances the phase of the VOR (in particular for relatively small frequencies of stimulation; 49). These deficits are largely replicated when the lesion is confined to the flocculus (50). Because these drastic procedures can have severe side effects and because the effects of chemical flocculectomy are less severe, there is no consensus concerning the participation of the cerebellum in velocity to position integration (51). In any case, the fact that the NIC, the NPH and the vestibular nuclei are not entrusted with all velocity to position integration in the oculomotor system is indicated by the fact that the versional eye position sensitivity of individual extraocular motoneurons differs from their vergence position sensitivity (52) which implies that the horizontal neural integrator(s) for conjugate eye movements differ(s) from the one for disjunctive eye movements (53).

4. DISCHARGE PATTERNS

4.1. NIC neurons

The discharge of NIC neurons has attracted considerable interest in both the cat and the monkey. NIC oculomotor related cells have been divided into burst-tonic (BT), irregular tonic (IrT) and burst (BN) neurons in the monkey (54), and into burst-tonic (BT), pitch and vestibular-and-saccade (VSN) neurons in the cat (55). The firing rate (F_R) of NIC cells which carry eye position information is described by the expression,

$$F_R = F_0 + kE + r\dot{E} \qquad (1)$$

where F_0 is the neural discharge at primary position, k and r constants which differ for different cells, and E is the instantaneous position of the eyes (usually in the vertical plane). In the cat, only 2 out of 41 cells (about 5%), were found to encode eye position along an oblique direction (determined from the arc of tangent equal to the ratio of the slopes of the vertical and the horizontal rate-position curves; 55).

Considerable effort has been invested in estimating the parameters of Eq. 1. Values obtained by different labs in the cat and the monkey are summarized in table 1. As implied by Eq. 1, NIC BT neurons often discharge tonically as long as the position of the eyes does not change. Depending on the constancy of the duration of successive interspike intervals, NIC cells can be separated into regular or irregular. The coefficient of variation (CV) of interspike intervals (i.e., the ratio of the standard deviation over the mean of the interspike intervals) has proved a useful descriptor in this regard. A CV of 0.2 has been used to separate regular from irregular cells in the cat (55). As has been demonstrated in the cat, the regularity (CV) is inversely related to the intensity (F_0) of a neurons discharge at primary position (figure 2A of ref. 55). Also, the tonic discharge of NIC cells has been shown to vary in proportion to the vertical deviation of the eyes from the primary position (with correlation coefficients between the two variables ranging between 0.6 and 0.9; ref. 55). The slope of the rate-position curve together with the parameter F_0 uniquely determine an NIC neuron's recruitment threshold; in the monkey, this ranges between -78 and -3 (negative sign indicates off-direction) with an average value equal to -31 ± 10 (±SD; ref. 54).

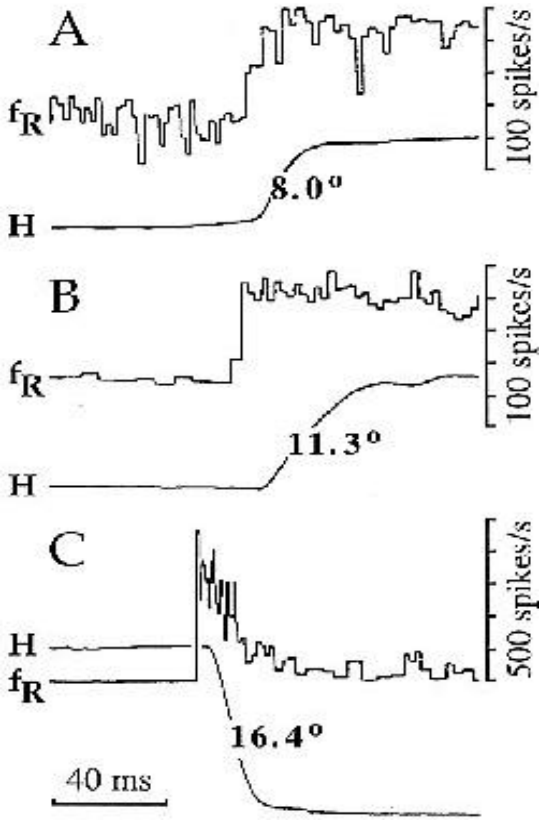

Figure 2. Discharge pattern of position (A) position-velocity (B) and velocity-position (C) neurons of the nucleus prepositus hypoglossi (modified from ref. 60, with permission). Traces are instantaneous horizontal eye position(H) and firing rate (f_R). Numbers on top of the eye position trace indicate the size of saccades.

As implied by Eq. 1, NIC BT cells often emit a burst of discharges for saccades in their preferred direction (again usually either up or down). Latencies range from 34 to -4 ms in the cat (mean±SD: 10±3 ms; ref. 55) and from 8.9 to -1.4 ms in the monkey (mean±SD: 4.0±2.5 ms; n = 17; ref. 54). The number of spikes in the burst (N_b) of NIC cells is positively correlated with the amplitude of saccades; correlation coefficients are in the 0.4 - 0.6 range (55). Neither feline nor primate NIC cells pause consistently for off-direction saccades. Pauses have often been described as little more than a few increased interspike intervals in the monkey (54). In the cat, they are absent in some cells and not consistent in the remaining cells (55). The intensity of saccade related discharges of NIC BT cells has been carefully analysed to determine whether they cluster into distinct subclasses. To this end, Fukushima and his colleagues (55) defined the burst index, i.e., the maximal frequency of a neuron's discharge during on-direction saccades minus its postsaccadic rate of discharge. The burst index of feline NIC BT cells was found to range between 8 and 352 spikes/s (average: 135 spikes/s). It was further found to covary with other parameters of discharge; thus, the more regular the cell (i.e., the lower the CV) and the higher its intensity at primary position (i.e., the higher the F_0) the more intensely did it discharge for saccades in its on-direction (55). Although a burst index value of 60 spikes/s could separate tonic from burst-tonic neurons (55), the burst indexes of NIC cells could equally well support the notion that they form a continuum with varying degrees of burstiness.

The discharge of primate IrT and of feline pitch cells is also related to eye position, albeit weakly. Only, about 25% of the feline pitch cells modulate their discharge for vertical eye position (55). Studies of the adaptive gain changes of the VOR induced by tenectomy of the vertical recti in one eye indicate that BT and pitch neurons also differ in terms of the behavioral relevance of their discharge (56). Continuous low frequency sinusoidal pitch rotation with the normal eye covered produces a gradual and significant increase of the VOR gain of the normal eye (by about 50%) within about one hour from the onset of rotation. The firing rate of all (n=9) vertical BT showed a significant gain change (by 56% on the average) that preceded the increase of the VOR gain, while only one (out of 9) pitch cells showed a similar increase. As with feline pitch cells, the discharge of primate irregular tonic (IrT) neurons displays little if any relationship with eye position at least during spontaneous saccades (54). Also, their discharge is unmodulated during VOR suppression which implies that IrT cells do not receive any head velocity information.

The NIC and the surrounding reticular formation contain additional cell classes such as feedback MLBs (8), LLBs with descending projections to the pons (57), Vestibular and Saccade Neurons (VSNs; ref. 19) and Burster-Driver Neurons (BDNs; 58, 59). Because their discharge is not modulated in between saccades, MLBs and LLBs of the NIC are unlikely to contribute directly to the position sensitivity of vertical motoneurons and will not be further considered. Readers should consult the original literature for a description of the response properties, axonal trajectories and pattern of axonal terminations of these cells (8, 57).

The response properties of VSNs have been studied in the cat by Fukushima and his colleagues (19). VSNs emit a burst of discharge before saccades or quick phases in the direction they prefer (up or down). Latencies of VSN bursts are in the long-lead range (35±14 ms). The number of spikes in the bursts is correlated with the amplitude of the vertical saccadic component in about half of the VSNs examined (r: 0.6 - 0.7, n = 16), and burst duration is correlated with saccade duration (r: 0.5 - 0.6). Remarkably, about half of the cells that burst for downward saccades also modulate their discharge in proportion to upward eye position, albeit not consistently and only if periods of time shortly before or after saccades are examined. In general their discharge at primary position is irregular (CV = 0.5±0.31, mean±SD; range 0.09 - 1.29) and lower than that of BT cells (F_0 = 40±18 spikes/s, mean±SD; range: 9 - 85 spikes/s; ref. 19). Finally, upward (downward) VSNs emit short latency responses to electrical stimulation of the contralateral vestibular nerve and pitch head rotation. Consistent with this, their modulation during sinusoidal head rotation precedes eye position by 58 deg (range: 20 - 100).

4.2. NPH neurons

The discharge pattern of a large sample (n =

Table 2. Relationship between the discharge of NPH neurons and parameters of ocular movement

Cell Type		species	N	k (spikes/s/deg)	F_0 (spikes/s)	CV	r (spikes/s/deg/s)	fi (deg)	Ref
PV/VP/P	(mean ±SD)	cat	24	4.15±1.9	65.8±46		<2 - 8[c]		60[f]
	(range)			1.1-7.5	0-173				
P	(mean ±SD)	cat	6	7.3±2.7			0.16±0.11[a]		61
	(range)			2.7-9.6			0.03 - 0.36		
PV	(mean ±SD)	cat	10	5.2±3.7			0.62±0.37[a]		61
	(range)			1.2-11.6			0.26 - 1.4		
VP	(mean ±SD)	cat	6	2.1±1.7			0.75±0.19[a]		61
	(range)			0.1-4.5			0.53 - 1.1		
PH_e	(mean ±SD)	cat	10	8.2±2.9	7.5±2.1	0.2±0.5	0.15±0.21[a]	11.3±4.1	68
	(range)						1.0±0.7[c]		
PH_i	(mean ±SD)	cat	9	7.9±2.9	-6.0±1.5	0.2±0.4	0.32±0.28[a]	13.0±4.5	68
	(range)						0.8±0.3[c]		
SC_t	(mean ±SD)	cat	12	5.17±3.26	40.7±21.8		1.26±0.62[a]		67
	(range)			1.9-11.5	14.9-84.4		0.38 - 2.12		
BT	(mean ±SD)	monkey	51	3.2±1.3	54.7±43.2		0.96±0.48[b]	36.8±14	64
	(range)			1.2 - 6.4					
T	(mean ±SD)	monkey	19	2.4±1.6	56.6±31.3		0.39±0.2[b]	23.7±8.9	64
	(range)								
EHV	(mean ±SD)	monkey	14	1.5±1.1	47.4±40.8		1.13±0.76[b]	61.1±24.6	64
	(range)								

Abbreviations. a: Computed from the peak rate vs. peak velocity relationship; b: Computed from smooth pursuit; c: Computed from vestibular slow phases; f: Computed from the values given in Table 1 of ref. 60; EHV: neurons encoding eye and head velocity; P: neurons encoding eye position; PH_e: excitatory cells of the NPH; PH_i: inhibitory cells of the NPH; PV: neurons encoding eye position and eye velocity; SC_t: neurons that project to the superior colliculus; T: tonic neurons, VP: neurons encoding eye velocity and eye position. Other abbreviations as in Table 1.

118) of oculomotor related NPH cells was analysed in the cat by Lopez-Barneo and his colleagues (60). Their salient features (figure 2) include modulation of their discharge together with the intersaccadic position of the eyes, more or less intense bursts for saccades in the same direction (horizontal ipsiversive for about 60% of the cells) and rate decreases for saccades in the opposite direction. Whenever present, the bursts of NPH cells precede saccades by about 5 ms on the average and their duration is roughly equal to that of the saccades they accompany. As with NIC cells, their firing rate is quantitatively described by the expression,

$$F_R = F_0 + kE + r\dot{E} \qquad (2)$$

where F_0, k and r have the same meaning as in Eq. 1, and acquire different values for different cells. With the exception of a substantial minority of vertical (20/118, i.e., 17%) and oblique (28/118, i.e., 24%) cells (60), the variable E refers to the horizontal position of the eyes.

Lopez-Barneo and his colleagues (60) divided their sample of NPH cells into position (P) cells, position-velocity (PV) cells and velocity-position (VP) cells. Cells with the highest sensitivity for position (P cells) were the most regular and emitted the smallest bursts for saccades. At the other extreme, VP cells had the smallest position gain, they were the least regular and emitted considerable bursts for saccades. Values obtained by the parameters of Eq. 2 are summarized in table 2 separately for different types of NPH cells. figure 3A illustrates the position of 22 NPH cells which were described in a later study of the same group (61), in a 2-D scatterplot of rate-position correlation coefficient versus rate-velocity correlation coefficient. The vertical line, passes through 0.6 which is the value of the correlation coefficient between rate and position used to separate the P and PV cells from the VP cells. Similarly, the rate-velocity regression coefficient of 0.6 was used to separate the P from the PV cells. Arguably, the two correlation coefficients are inversely related (figure 3A) and the cells form a continuum from VP (top left) to P (bottom right) through PV (top-right) cells. The regularity of discharge also increases in the same direction, from VP to P cells. Representative neurons (illustrated in figure 11 of ref. 61) had a coefficient of variation (CV) equal to 0.18 (P cells), 0.22 (PV cells) and 0.34 (VP cells). However, NPH cells could have been grouped differently (figure 3D) if the slopes of the rate-position and rate velocity curves had been used instead of the correlation coefficients despite the fact that the slopes are correlated with the correlation coefficients in both the rate-position (figure 3B) and rate-velocity (figure 3C) curves.

Additionally, the feline NPH contains cells whose discharge pattern resembles that of NIC Burster-Driver Neurons (BDNs; ref. 62). BDNs emit a burst of discharges before all quick phases which accompany contraversive horizontal head rotations (63). Their discharge decreases for ipsiversive quick phases as does their slow phase discharge during ipsiversive rotations (type II response). BDNs also emit bursts of discharges for contraversive, horizontal spontaneous saccades. The onset of the burst is gradual but its high frequency portion precedes saccades or quick phases by a fairly long lead (30-50 ms). As with MLBs and several classes of LLBs, highly significant correlations obtain between the number of spikes in BDN bursts and the size of horizontal saccades or quick phases. However, unlike other other burst neurons, BDNs display a relatively high, tonic irregular discharge during intersaccadic intervals (63). No relationship between this tonic discharge and the intersaccadic position of the eyes has been established. Because of their projections towards the NRTP, the EBN and the IBN areas of the opposite side of the brain (62), BDNs are more likely to supply the burst generators with saccade related information rather than participate in the process of neural integration in the saccadic system.

A roughly similar gamut of cells has been encountered in the primate NPH (64). Eye position related neurons located in and around the primate NPH have been separated into three groups: burst-position (BP), position (P), and eye-head velocity cells (EHV).

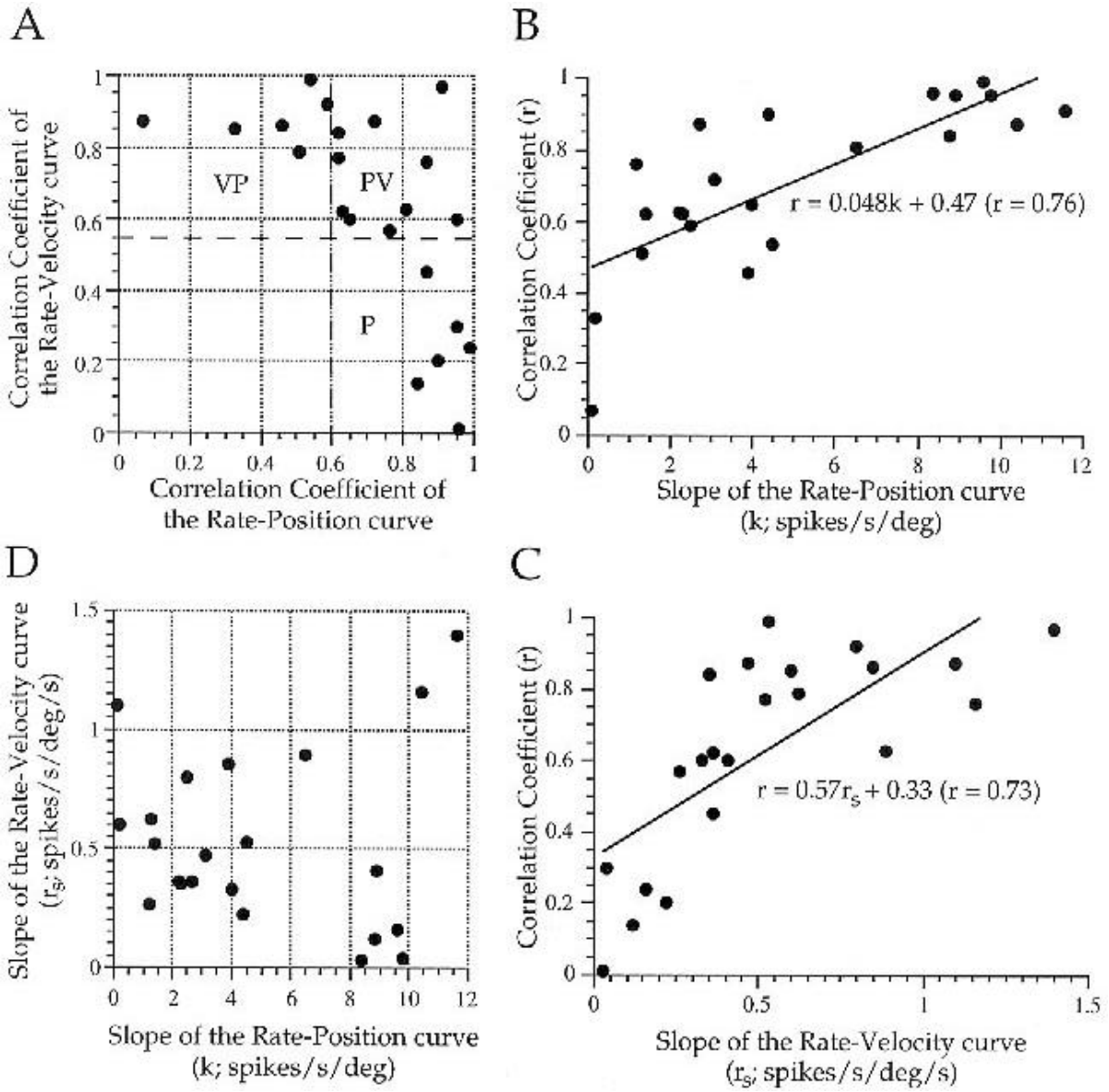

Figure 3. 2-D plots of the relationship between the position sensitivity (k) and the velocity sensitivity (r_S) of NPH cells (each solid circle corresponds to one neuron (prepared from data in table 3 of ref. 61). (A) Plot of the correlation coefficient between firing rate and eye velocity (ordinate) vs. the correlation coefficient between firing rate and eye position (abscissa). (B) Plot of the correlation coefficient between firing rate and eye position (r; ordinate) vs. gain of position sensitivity (k; abscissa). (C) Plot of the correlation coefficient between firing rate and eye velocity (r; ordinate) vs. gain of velocity sensitivity (r_S; abscissa). (D) Plot of the gain of velocity sensitivity (abscissa) vs. gain of position sensitivity (ordinate).

BP cells are the more numerous (three times more numerous than the P and EHV cells) and are the only ones encountered in a sub-area of the hypoglossal complex called marginal zone. BP, P and EHV cells modulate their discharge in proportion to ipsilateral eye position; quantitative estimates of their eye position sensitivity are summarized in table 2. The correlation coefficient between eye position and the firing rate of P and BP cells is typically greater than 0.6 and can be as high as 0.99 (64). The eye position sensitivity of NPH cells is correlated with their recruitment threshold so that the further away from its on-direction a cell's threshold is the lower its position sensitivity (slope = 0.042, r = 0.61; ref. 64). Thresholds computed on the basis of the slope of the rate-position curve (table 2, column 4) and the discharge at primary position (table 2, column 5) range between more than 65 deg in the off-direction to 11.1 deg in the on-direction for BP cells (mean±SD:-20.5±17.9 deg), more than 100 in the off-direction to 0 deg in the on-direction for P cells (mean: -32.2±23) and even further in the off-direction for EHV cells (mean: -49.5±51.2 deg; ref. 64).

The BP cells and about 60% of the EHV cells also emit a burst that precedes on-direction saccades by 7.6 ± 1.7 ms (mean ± SD; n = 15). Burst duration is well

correlated (r = 0.95±0.03; n = 11) and roughly equal to saccade duration. The number of spikes emitted during such bursts is also well correlated with the size of the horizontal component of saccades (r = 0.9±0.05 mean ± SD, range: 0.8-0.98) and amount to 0.77±0.28 (mean±SD) spikes per degree of eye displacement. Off-direction saccades are accompanied either by a step decrease in discharge or a pause which is often little more than a few longer interspike intervals. Whether burst-position cells will pause for saccades in their off-direction seems to depend on their location; it is often the case for MVN/NPH cells but almost never for marginal zone cells.

Additionally, NPH cells have been shown to modulate their discharge in proportion to the velocity of the eyes during vestibular and pursuit eye movements; quantitative estimates of their eye velocity sensitivity are summarized in table 2. Further, the phase shift of the signal carried by BP cells (table 2, column 8) is in between that for position (0 deg) and velocity (90 deg), while that of P cells is biased towards eye position and that of EHV cells towards eye velocity. To test whether this modulation reflects eye velocity or head velocity information the discharge of NPH cells was evaluated while trained monkeys suppressed their VOR responses (64). Under such conditions, no vestibular sensitivity was seen in either BP or P cells whereas EHV cells were modulated roughly in phase with head velocity (leading it by 12±17 deg, on the average, at 0.5 Hz, n = 18); usually (75%) EHV cells display a type I response, i.e., their discharge increases for rotation towards the ipsilateral side. Accordingly, the discharge pattern of EHV cells is reminiscent of that of floccular gaze-velocity Purkinje cells (65, 66); unlike Purkinje cells, the eye velocity gain of EHV cells is 1.5 times bigger than their head velocity gain (64). EHV cells have not been found in the feline NPH. However, because of their tonic discharge, their saccade related bursts and their head velocity sensitivity, feline BDNs have been thought to correspond to primate EHVs (16). Differences between BDN and EHV cells (the latter carry eye position information while the former do not, the latter show type I and the former type II responses to head rotation) have not been deemed severe enough to undermine this suggestion. After all the position sensitivity of EHV cells is so small that it could have been missed in untrained cats.

Is the classification of NPH cells into BT, TB, T and EHV (or BDN) a natural one, as suggested by some authors (64), or is it a convenient way to break down a continuum of discharge patterns for presentation purposes, as suggested by others (61)? It is more likely to prove a natural one if cells with different discharges differ in other respects as well (e.g., somatodendritic morphology, pattern of projections, etc.). To explore this issue, Delgado-Garc'a and his colleagues (61) determined the axonal projections of a sample of NPH cells by backfiring them from several targets of the NPH. Of the 6 oculomotor related cells that were seen to project to the ipsilateral NIC one was a VP, 2 were PV and 3 were P. Of the 8 that were seen to project through the posterior cerebellar peduncle, two were PV and 6 were VP. Finally, of the 20 that were antidromically identified from the MLF, 10 were VP, 7 were PV and 3 were P. Of the 4 that were seen to project to the SC, one was a PV and 3 were P. The discharge properties of the very small percentage (less than 4%) of oculomotor related NPH cells that project to the superior colliculus have been also studied by Hardy and his group (SC_t cells, table 2; ref. 67). They presumably correspond to VP and PV cells because of the bursts they emit prior to saccades (mean latency ± SD: 14.7±3.6; range: 9.5 - 19.9 ms; n = 8). Apparently, whatever differences exist in terms of projections of distinct functional classes of feline NPH neurons are rather subtle. Nevertheless, they can be ferreted out as recently demonstrated by Delgado-Garc'a and his group (68). These authors employed electrical stimulation of the ipsilateral and the contralateral abducens nucleus to physiologically identify NPH cells. They were thus able to implicate type II P cells of the rostral third of the NPH in a preferential projection to the abducens nucleus (68). Finally, the same authors were able to demonstrate the existence of a monosynaptic connection between P cells of the NPH and abducens motoneurons after establishing that the latencies of the average field potentials recorded in the abducens nucleus and triggered from spikes of P cells (these corresponded to EPSPs or IPSPs when triggered from spikes of ipsilateral or contralateral cells, respectively) ranged between 0.7 and 0.9 ms (mean±SD: 0.76±0.05 ms, n = 4) while the average latencies of the antidromic responses of NPH cells were equal to 0.23 ± 0.07 ms and 0.37 ± 0.12 ms (mean ± SD) for ipsilateral and contralateral cells, respectively.

4.3. Secondary vestibular neurons

Because of their pattern of discharge and their projections, secondary vestibular neurons are eminently qualified to supply extraocular motoneurons with some of the eye position signal they carry. Besides participating in the VOR, secondary vestibular neurons would thus participate in the velocity to position integration in the saccadic and optokinetic systems. The relationship between their firing rate (f_R) and parameters of ocular movement is described by the expression,

$$F_R = F_0 + kE + r\dot{E} + g\dot{H} \qquad (3)$$

where F_0, k and r have the same meaning as in Eqs. 1 and 2, and g is the gain re instantaneous head velocity ($\dot{H}$).

Several classes of vertical secondary vestibular neurons have been described in alert behaving monkeys. These differ in terms of the behavioral relevance of their discharge. Thus, there are pure vestibular (V) cells which discharge in proportion to head velocity in space, vestibular-pause (VP) cells which discharge in proportion to head velocity and pause for saccades, gaze-velocity (GV) cells which discharge in proportion to eye velocity in space, position (P) cells which discharge in proportion to eye position and eye velocity in the head, position-vestibular (PV) cells which discharge in proportion to eye position, eye velocity and head velocity, burst-position (BP) cells which discharge in proportion to eye position in the head, and burst somewhat or pause for saccades (in the on- and off-direction, respectively), and position-vestibular-pause cells (PVP) which discharge in proportion to eye position and head velocity while they pause for all saccades (69). The parameters which describe the discharge of the cell

classes that carry eye position information (PV, P, BT and PVP) as per Eq. 3 are shown in table 3. The PV and the P cells correspond to the vestibular plus eye position ($E_V{}^{+H}{}_V$) and the pursuit ($E_V{}^{+\dot{E}}{}_V$) cells of (70). Besides eye position, these cells fire in proportion to eye velocity while the former discharge in proportion to head velocity as well with a mean gain, g, equal to 1.0 spike/s/deg/s, range: 0.2 - 2.4 spikes/s/deg/s). In addition, both cell types usually pause for saccades (latency 8.2±1.7 ms, range: 5.6 - 10.9) or show no change in firing frequency (70). PVP cells also carry head velocity information to the tune of 1.1 spikes/s/deg/s (range: 0.7 - 1.9; ref. 69).

Other cells that could provide motoneurons with an eye position signal, albeit small (range: 0 - 1.3 spikes/s/deg; ref. 69), are the vertical gaze velocity cells of the group Y. Their discharge is modulated almost in-phase with upward eye velocity during pursuit with the head still and upward head velocity during VOR cancellation, but is not modulated during VOR in the dark (71, 69, 72). Other parameters that describe their discharge as per Eq. 3, have as follows: mean F_0 equals 106 spikes/s (range: 79 - 137 spikes/s), mean r equals 1.1 spikes/s/deg/s (during smooth pursuit; range: 0.6 - 1.7) and mean g during VOR cancellation equals 0.93 spikes/s/deg/s (range: 0.3 - 1.5). The r and g terms are such that they effectively cancel out during VOR cancellation rendering the cells modulation negligible. Group Y cells also emit irregular bursts for most vertical saccades (both up and down) the intensity of which does not seen related to saccade metrics (69). The importance of the influence they exert upon motoneurons is indicated by the fact that the adaptation of their discharge can account for the phenomenon of VOR adaptation (72). Group Y cells are excitatory glutamatergic ones and project to the IO and SR subdivisions of the oculomotor nucleus (73, 74, 75, 76). The eye velocity signal they carry could be integrated into an eye position signal via their additional projections to the NIC (77, 78).

Let us now turn to the horizontal system. Here again, several classes of secondary vestibular neurons have been described in alert behaving monkeys (79). These are largely located in the medial vestibular nucleus and can be distinguished into pure vestibular (V) cells which discharge in proportion to head velocity, eye/head velocity (EHV) cells which discharge in proportion to eye velocity and head velocity and emit vigorous bursts for saccades in their on-direction (while they pause for saccades in the opposite direction), eye position (P) cells which discharge in proportion to eye position and eye velocity and often pause for off-direction saccades, burst-position (BP) cells which discharge in proportion to ipsiversive (usually) eye position and eye velocity, and burst or pause for saccades (in their on- and off-directions, respectively), and position-vestibular-pause cells (PVP) which which discharge in proportion to eye position in the head and head velocity in space. PVPs usually pause for all off-direction saccades (latency 13.3±3.8 ms) and the duration of their pauses usually exceeds the duration of the saccade. However, some cells do not pause for off-direction saccades while about half of them neither pause nor burst for saccades in their on-direction. The remaining half, either burst slightly or pause for saccades in the on-direction. The parameters that describe the discharge of horizontal secondary vestibular cells which carry eye position information (P, BP, PVP. EHV) are summarized in table 3 and the pattern of connections that they establish with extraocular motoneurons is considered in Section 5.5.

5. INPUT-OUTPUT CONNECTIONS

To play the role expected of them, the neural integrators of the saccadic system must receive input from medium lead burst neurons (MLBs) and send their output to motoneurons. The discharge pattern of integrator cells is compared to that of MLBs in Section 5.1 and to that of motoneurons in Section 5.3. Evidence that supports the existence of connections between the vertical (and horizontal) MLBs and the neural integrators is presented in Section 5.2 while connections between the neural integrators and extraocular motoneurons are described in Section 5.4. Because some of the motoneuronal position sensitivity could be due to signals they receive from secondary vestibular neurons, projections of secondary vestibular neurons to motoneurons are described in Section 5.5. The NIC, the NPH and the vestibular nuclei could collectively form a distributed network that carries out the process of integration; interactions between these nuclei are described in section 5.6.

5.1. Comparison with MLBs

Medium lead burst neurons (MLBs) are instrumental for providing the neural integrators with the pulse of activity they need to integrate. In alert animals, MLBs discharge before and during rapid eye movements (typically, latencies are less than 12 ms). MLBs can be divided into several subclasses on the basis of their preferred direction, the location of their somata, the trajectory of their axons and the excitatory or inhibitory influence they exert on their targets. On the basis of their preferred directions, MLBs of each half of the brain can be divided into three separate groups: 1) horizontal ipsilateral, 2) upward and 3) downward. The horizontal MLBs encode the size of horizontal saccadic components and are located in the PPRF near the abducens nucleus (3, 4, 80-83). The upward and downward MLBs (UMLBs and DMLBs) encode the size of vertical saccadic components and most of them are located in the riMLF of the rostral mesencephalon (5-9, 54, 84, 85). Each one of the three groups of MLBs (horizontal, up and down) is further subdivided into excitatory and inhibitory neurons. In the case of horizontal cells, these are referred to as EBNs and IBNs, respectively.

There are strong projections of vertical MLBs (VMLBs) onto vertical motoneurons (#1, figure 4) as well as of horizontal MLBs (HMLBs) onto horizontal motoneurons (#3, figure 4). These will not be considered here as they have been considered in recent reviews (1, 86, 87). Suffice it to say that excitatory MLBs are one of the strongest sources of saccade related input to motoneurons. Accordingly, their discharge pattern carries enough information to specify parameters of saccades. The strongest correlation between a parameter of discharge and a saccadic parameter is the one between

Table 3. Relationship between the discharge of vestibular neurons and parameters of ocular movement

VERTICAL CELLS

Cell Type		species	N	k (spikes/s/deg)	F_0 (spikes/s)	CV	r (spikes/s/deg/s)	fi(deg)	Ref
DPV	(mean ±SD)	cat	131	3.2±1.3	59±31	0.24±0.08		53.4	130
	(range)			1.2-9.1	-45-124	0.12-0.5		27.6-71.7	
$E_u+\dot{H}_d$	(mean ±SD)	cat	9	2.4	107			86.4	130
	(range)			1.2-3.3	79-128			66.8-106.9	
$E_v+\dot{E}_v$	(mean ±SD)	monkey	25	1.9±1.2	102±42		0.36±0.3[b]	37±33	70
	(range)			0.49-5.6	11-174		0-0.88	-5 - 137	
$E_v+\dot{H}_v$	(mean ±SD)	monkey	10	1.9±1.3	79±31		0.52±0.42[b]	36±26	70
	(range)			0.32-4.1	2-109		0-1.2	-5 - 83	
PV	(mean ±SD)	monkey	53	1.1	72		0.4[b]		69
	(range)			0.4-3.4	25-136		0-1.5		
P	(mean ±SD)	monkey	36	1.1	67		0.4[b]		69
	(range)			0.3-2.5	11-93		0.1-1.8		
BP_v	(mean ±SD)	monkey	42	1.7	68		0.6[b]		69
	(range)			0.7-3.7	22-122		0.3-1.8		
PVP_v	(mean ±SD)	monkey	55	2.4	115		0.4[b]		69
	(range)			0.6-3.9	72-156		0-1.0		

HORIZONTAL CELLS

Cell Type		species	N	k (spikes/s/deg)	F_0 (spikes/s)	CV	r (spikes/s/deg/s)	fi(deg)	Ref
MV_i	(mean ±SD)	cat	6	2.2±1.3	44.1±6.8	0.35±0.5	0.15±0.07[a]	80.2±12.5	68
	(range)						1.5±0.3[c]		
MV_e	(mean ±SD)	cat	10	1.8±0.9	40.7±7.9	0.2±0.4	0.17±0.15[a]	86.0±14.1	68
	(range)						1.6±0.2[c]		
$E_h+\dot{H}_h$	(mean ±SD)	monkey	21	1.4	81			105	36
	(range)			0.3-3.3	0-140			90-125	
BP_h	(mean ±SD)	monkey	7	2.4				20.5±6.4	36
	(range)			1.2-5				10-60	
PVP_h	(mean ±SD)	monkey	69	1.73±0.93			0.53±0.38[b]		79
	(range)			0.24-4.7					
BP_h	(mean ±SD)	monkey	11	3.6			1.1[b]		79
EHV	(mean ±SD)	monkey	33	1.97±2.0			2.2±2.1[b]		79
	(range)			-2.0 - 7.2			0.64-12.7		

Abbreviations. a: Computed from the peak rate vs. peak velocity relationship, b: Computed from smooth pursuit, c: Computed from vestibular slow phases, $E_v+\dot{E}_v$: Vertical Pursuit neurons, MV_i: Inhibitory cells of the medial vestibular nucleus, MV_e: Excitatory cells of the medial vestibular nucleus, $\dot{H}_h$: Horizontal head velocity cells, $E_h+\dot{H}_h$, $E_u+\dot{H}_d$, $E_v+\dot{H}_v$: Vestibular plus position cells with horizontal (h), vertical (v) up (u) or down (d) preferred directions, BP_h, BP_v: Burst-tonic cells with horizontal (h) or vertical (v) preferred directions, DPV: Downward position vestibular cells, EHV: Horizontal eye and head velocity cells; PV: position plus vestibular cells, P, position cells, PVP_h, PVP_v: horizontal (h) or vertical (v) position vestibular pause cells. Other abbreviations as in table 1.

the number of spikes in the burst (N_b) and the amplitude of the horizontal or vertical component of saccades (average values in different samples of MLBs range from 0.65 6 to 0.99 88). On the average, the slope of this relationship can be as high as 2.3 (89) or as low as 0.68 spikes per degree of eye displacement (88). Values obtained in other laboratories are summarized in table 4. Secondly, there is a roughly 1:1 relationship between MLB burst duration (B_d) and saccade duration (S_d), whatever the animal species or the cell type (rhesus EBN, ref. 2; rhesus IBN, ref. 90; cat IBN, ref. 83; squirrel monkey EBN, ref. 4). Finally, the average firing rate of MLBs is well correlated with the peak horizontal or vertical velocity of the eyes. Typical average slopes of these relationships equal 0.5 spikes/s per degree/s for monkey EBNs (89) and 0.36±0.24 spikes/s per degree/s for cat EBNs (91). These relationships are due to the connections that these cells establish with extraocular motoneurons and reflect properties of the burst generating networks in which they participate.

5.2. MLB projections to the neural integrators

The existence of connections between vertical MLBs and the vertical velocity to position integrator (#2, figure 4) is supported by evidence indicating that intraaxonally HRP injected axons of single functionally identified vertical MLBs ramify extensively within the NIC, on occasion bilaterally (7, 8). Similarly, the existence of connections between horizontal MLBs and the horizontal velocity to position integrator (#4, figure 4) is supported by the disclosure of ipsilateral PPRF projections to the regions that house the horizontal neural integrator (the VN/NPH complex) in retrograde (92, 93, 94, 95) and anterograde (96, 97, 98, 99, 100) tract tracing studies. The pattern of termination of individual intraaxonally HRP injected primate EBN axons in the VN/NPH complex also supports this notion (3). Figure 4 does not include connections between burst generators and neural integrators with opposite on-directions. Such inhibitory connections could account for the bi-directional modulation of the neural integrators. The existence of a connection between the IBNs of one side and the HNI of the opposite side is supported by the disclosure of projections from the IBN area of the reticular formation of the medulla to the contralateral VN/NPH complex with the help of retrograde (94, 95) and anterograde (97) tract tracing techniques. It is also supported by the disclosure of antidromic IBN responses to the electrical stimulation of the VN/NPH complex in the cat (82). Also, peri-spike time histograms of prepositus and vestibular nucleus neurons (specifically, type II neurons) aligned on single spikes of IBNs, demonstrate that the activity of the former is depressed

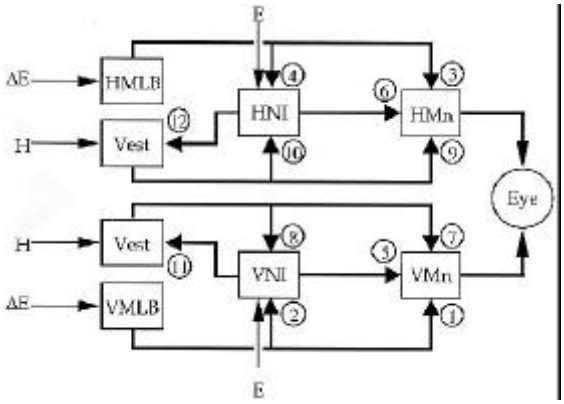

Figure 4. Schematic diagram of the input-output connections (arrows) of the neural integrators of the mammalian saccadic system. Evidence to support their existence is summarized separately for each one of them (identified by numbers in circles) in Section 5. Abbreviations: DE, eye displacement; $\dot{E}$, eye velocity; $\dot{H}$, head velocity; HMLB, horizontal medium lead burst neurons; Vest, vestibular nuclei; VMLB, vertical medium lead burst neurons. Other abbreviations as in figure 1.

when the latter discharge (82). Finally, it is supported by the fact that the terminal fields of single functionally and morphologically identified IBNs are distributed in the contralateral medial vestibular nucleus and the nucleus prepositus in both the monkey (3) and the cat (83). Apparently, the circumscribed region in the squirrel monkey VN/NPH complex that receives a heavy projection from ipsilateral EBNs, namely the region of the medial vestibular nucleus immediately caudal to the abducens nucleus, also receives input from contralateral IBNs (3).

5.3. Comparison with motoneurons

Extraocular motoneurons emit bursts of spikes for saccades in the pulling direction of the muscle they innervate and discharge tonically in proportion to the eye position reached at the end of the saccade. In general, their discharge can be described by the expression,

$$F_R = F_0 + kE + r\dot{E} \qquad (4)$$

where F_0, k and r have the same meaning as in Eqs. 1 and 2. The values they obtain for different motoneurons have been estimated in several labs for both the cat and the monkey (summarized in table 5).

Abducens motoneurons have been the object of particular interest. Their average position sensitivity (column 4, table 5) is somewhat higher in the cat (range: 4.4 - 8.7 spikes/s/deg) than in the monkey (range: 3.5 - 6.2 spikes/s/deg). It is also higher than the average position sensitivity of burst-tonic NPH neurons (cat: 2.1 - 8.2 spikes/s/deg; monkey: 2.4 - 3.2 spikes/s/deg; column 4, table 2). In the cat, recruitment thresholds of abducens motoneurons are close to the primary position (mean±SD: -3.3 ± 5.2 deg, range: -19 to 7; ref. 101). Their relatively low firing rate at primary position (column 5, table 5) is due to the fact that several cells start firing at positions more lateral than the primary position (these occupy the range between -78 and 0 spikes of table 5). The discharge of primate abducens motoneurons at primary position (36-108 spikes/s; column 5, table 5) is higher than that of NPH cells in the same species (47-57 spikes/s; column 5, table 2) as well as that of abducens motoneurons in the cat (about 23 spikes/s on the average; ref. 101). This could be due to the contralateral eye positions occupied by the recruitment thresholds of primate abducens motoneurons. Early estimates of the recruitment threshold of primate abducens motoneurons ranged from extreme medial (40 - 45 deg in the off-direction) till between 10 - 25 deg lateral (102, 40). More than half of the units had been recruited by the time the eyes reached 20 deg in the off-direction and all of them were recruited at primary position (threshold range: -60 deg to -5 deg) in a more recent detailed study of 39 abducens nucleus neurons (103). Similar is the picture emerging from yet another study of abducens motoneurons (104); here, thirty per cent of the abducens motoneurons were already active while the eyes were adduced by 45 deg and all units but one were active at primary position. Consistent with the notion that bigger abducens motoneurons are progressively recruited as the eyes occupy more abducting positions (size principle), the slope of the rate position curve has been found to increase with the recruitment threshold (correlation coefficient: cat = 0.63, ref. 101; monkey = 0.81, ref. 104; 0.78, ref. 103) at a rate of 0.32 spikes/s/deg/deg in the cat (101) or 0.11 spikes/s/deg/deg in the monkey (103) as well as the conduction velocity of the cell (correlation coefficient: 0.46; ref. 101). A reasonable correlation (0.67) has also been found between the slope of the rate-velocity curve of primate abducens motoneurons and their recruitment threshold (104).

The average position sensitivity of vertical extraocular motoneurons (4.2 spikes/s/deg; ref. 54) is also higher than the average position sensitivities of tonic and burst-tonic NIC neurons (2.0 - 2.6 spikes/s/deg; column 4, table 1). Since the pulling directions of vertical muscles are not strictly vertical, a correlation between the discharge of vertical motoneurons and horizontal eye position should come as no surprise. Indeed, trochlear motoneurons modulate their discharge in proportion to the lateral angular deviation of the eyes as well as with downward eye position. The relationship however is variable and, with the exception of one cell (with a slope of 5 spikes/s/deg), the slope of the rate-horizontal-eye-position curve is much more shallow (<1.3 spikes/s/deg (105). Vertical motoneurons have a higher discharge rate at primary position (105 spikes/s; ref. 54) than the NIC cells (about 80 spikes/s; ref. 54). As in the horizontal system, the high rate of motoneurons at primary position could be due to their low thresholds. Early estimates of recruitment thresholds in a sample of 35 primate oculomotoneurons, ranged from 62 deg in the off-direction till 21 deg in the on-direction (10), while cells were recruited at a rate of 10% of the motoneuron pool for every 10 deg that the threshold moved in the pulling direction of the muscle they innervate. Similarly, 8/27 trochlear axons discharged for upward eye positions beyond 30 deg, 2 units were recruited at about 10 deg down, while the remaining 17 units were recruited somewhere in between (at a rate of 18% of the motoneuron pool for every 10 deg that the threshold moved downward; 105). A more recent study of 78 cells, has demonstrated that primate vertical motoneurons start being recruited at 97 deg in the off-direction and virtually all are active by the time the eyes reach primary position (mean threshold ± SD: -25 ± 18 deg; ref. 54). Further excursions of the eye in the on-direction are

Table 4. Relationship between the number of spikes in MLB bursts and saccade metrics (N_b = a˙deltaE˙cos(theta-fi)+b)

Cell type		Species	N	α (spikes/deg)	β (spikes)	fi	Ref
IBN	(mean ±SD)	Cat	22	1.74 ± 0.4	5	horizontal	83
	(range)			0.9 - 3.1			
IBN	(mean ±SD)	Monkey	19	1.9 ± 1.14		on-direction	3
IBN	(mean ±SD)	Monkey	29	1.3	4.4	horizontal	90
EBN	(mean ±SD)	Monkey	22	2.0 ± 1.0		on-direction	4
EBN	(mean ±SD)	Monkey	6	2.3		horizontal	89
	(range)			1.4 - 3.4			
EBN	(mean ±SD)	Monkey	19	0.68	7.3	horizontal	88
VMLB	(mean ±SD)	Monkey	44	0.94 ± 0.49		vertical	6
	(range)			0.02 - 3.2			
VMLB	(mean ±SD)	Monkey	20	0.97±0.34		vertical	159
UMLB	(mean ±SD)	Monkey	14	1.6 ± 1.1		vertical	7
	(range)			0.36 - 4.29	-0.7 - 9.6		
DMLB	(mean ±SD)	Monkey	29	1.0 ± 0.5		vertical	8
	(range)			0.27 - 2.56	-2.0 - 13.1		

Abbreviations. ϕ: direction used for the analysis; IBN: inhibitory burst neuron; EBN: excitatory burst neuron; DMLB: downward MLB; UMLB: upward MLB; VMLB: vertical MLB.

Table 5. Relationship between the discharge of extraocular motoneurons and parameters of ocular movement

Cell Type		species	N	k, (spikes/s/deg)	F_0, (spikes/s)	CV	r (spikes/s/deg/s)	fi, (deg)	Ref
VI MNs	(mean ±SD)	Cat	53					40	133
	(range)							30-80	
VI MNs	(mean ±SD)	Cat	40	8.7±2.5	22.7±4		1.13±0.45[a] or 1.31±0.34[c]		101
	(range)			2-17.7	-78 - 115	0.05-0.25	0.64 - 2.20[a] or 0.97 - 2.19[c]	10-20	
VI MNs	(mean ±SD)	Cat	12	4.4±0.8			0.81±0.22		160
VI MNs	(mean ±SD)	Cat	31	7.5±3.23					161
	(range)			3.31-15.43					
VI Ns	(mean ±SD)	Monkey	21	3.5 ± 1.2	~100	<0.1			104
	(range)			2.1 - 7					
VI Ns	(mean ±SD)	Monkey	39	5.1±1.8	99.8±31.3				103
	(range)			1 - 8.8	28.6 - 149.9				
VI MNs	(mean ±SD)	Monkey	81	6.2±3.1	36.3±71.7		0.94±0.3[b]	22.6± 4.9	162
	(range)			1 - 17.8					
VI Ns	(mean ±SD)	Monkey	67	3.5		0.06 (n= 16)	0.6[b]		102
	(range)			1.1 - 14.5		(0.04 - 0.14)	0.25 - 3.7		
VI Ns	(mean ±SD)	Monkey	14	5.6±2.5	108±103		0.91±0.62[b,f]		40
	(range)			3.3-12	-84 - 223		0.3 - 2.23		
VI Ns	(mean ±SD)	Monkey	28	4.6±1.3					52
	(range)			2.7 - 7.8					
MR MNs	(mean ±SD)	Monkey	33	5.3±2.0					52
	(range)			2.6 - 11.2					
III Ns	(mean ±SD)	Monkey	10	7.06±7.4	74±66		1.5±1.7[b]		10
	(range)			2.56- 25	0-172		0.35 - 5		
III MNs	(mean ±SD)	Monkey	20	1.7 - 20					106
IV MNs	(mean ±SD)	Monkey	27	2.2 - 12.5		<0.1			105
VMNs	(mean ±SD)	Monkey	78	4.2±2.3	105		0.6	37±7.5	54
	(range)			0.7 - 18.0				16-63	

Abbreviations. a: Computed from the peak rate vs. peak velocity relationship during saccades; b: Computed from smooth pursuit; c: Computed from vestibular slow phases; f: evaluated from Table 1 of ref. 40); III, oculomotor nucleus; VI: abducens nucleus; IV MNs: trochlear nucleus; MR MNs: medial rectus motoneurons; VMNs, vertical motoneurons. Other abbreviations as in Table 1.

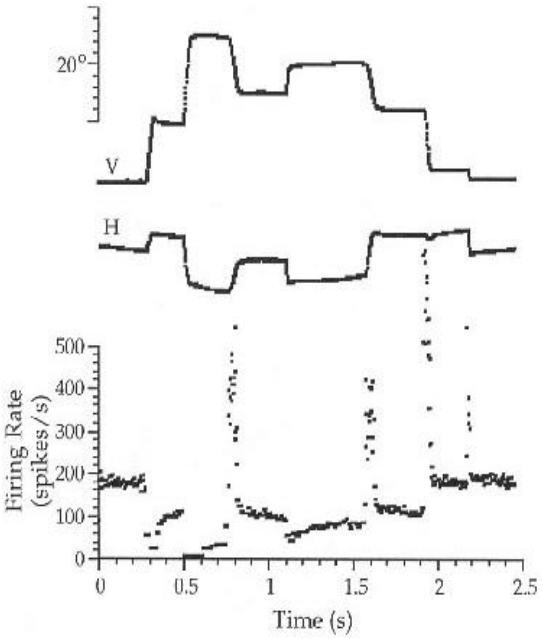

Figure 5. Discharge pattern of the NIC neuron illustrated in figure 7 (modified from ref. 115, with permission). Traces from top to bottom illustrate vertical (V) and horizontal (H) instantaneous eye position and instantaneous firing rate.

apparently due to an increase of firing rate alone. As with abducens motoneurons, the slope of the rate-position curve of both oculomotor (10) and trochlear motoneurons (105) has been found to increase with recruitment threshold.

The saccade related bursts of abducens motoneurons can reach up to a frequency of 200 - 830 spikes/s, (mean: 400 spikes/s; ref. 102) and precede saccades by 8.9±2.8 ms in the cat (101) and 5.4 ms in the monkey (102). There is a positive correlation between the peak frequency and the latency of abducens MN saccade related bursts. The higher the frequency reached by a unit the earlier it starts firing, so that abducens motoneurons that emit the most intense bursts can precede sluggish ones by as much as 3 ms (104). For saccades in the off-direction, activity decreases or pauses with a latency of 14.8 ± 4.05 ms in the cat (101) and 6.3 ms in the monkey (102).

The latency of bursts emitted by primate oculomotoneurons is somewhat shorter. On the average, they precede saccades by 4.4 ± 2.2 ms (mean±SD) when they are recorded inside the nucleus (54) or by 3 ms (range: 0 - 5.5 ms) when they are recorded from fibers of the trochlear nerve (105). These values do not differ from the mean latency of the bursts emitted by NIC

burst-tonic neurons (cf. Section 4.1) or vertical MLBs (84, 6, 7, 8) in the same species. The peak frequency reached during bursts differs from one MN to the next. Some trochlear motoneurons reach frequencies that do not surpass 200 spikes/s while others reach frequencies as high as 550 spikes/s; the peak frequency of most of them is in the range of 350 - 450 spikes/s (105). The same is true of oculomotoneurons; their peak frequencies can be as low as 150 spikes/s for some cells and as high as 620 spikes/s for other (mean: 377, n = 35). Actually, the histogram of maximum burst rates during saccades seems to follow a bimodal distribution with one peak at about 250 spikes/s and a second peak at about 400 spikes/s (10). As, with MLBs, the number of spikes emitted by extraocular motoneurons during such bursts is proportional to the size of saccades in their pulling directions; slopes range between 0.25 - 2.5 spikes per deg (r: 0.8 - 0.9, n = 20; ref. 106). For off direction saccades, units usually pause with a mean latency of 6.7 ms (range 2.5 - 11 ms; ref. 105). As with NIC cells, some primate oculomotoneurons slow down instead of pausing, in particular after presaccadic discharge rates higher than 100 spikes/s (105).

5.4. Integrator projections to motoneurons

The notion that the vertical neural integrator projects to vertical extraocular motoneurons is supported by considerable evidence. Older efforts to demonstrate NIC projections to vertical extraocular motoneurons involved electrical lesion or stimulation of the NIC to visualize degenerating fibers into the oculomotor nucleus in the monkey (107) and the cat (108), or record PSPs intracellularly from vertical extraocular motoneurons in the cat (109). These results were not compelling because fibers originating elsewhere (e.g., from UMLBs and DMLBs) and deploying terminal fields in areas occupied by vertical extraocular motoneurons can be lesioned or activated inside the NIC. Recent results provide more confidence in the existence of connections between the NIC and contralateral oculomotor and trochlear nuclei (#5, figure 4). Their existence is supported by autoradiographic evidence in the cat (110) and the retrograde labelling of NIC neurons (mainly contralaterally) following bulk injections of HRP in the oculomotor nucleus of several mammalian species (rabbit, 111; cat, 112; monkey, 5, 73). Moreover, it is supported by the recovery of transynaptically labeled NIC neurons after the retrograde transport of tetanus toxin injected into the IO and IR muscles of the rabbit (113). Finally, injections of PHA-L and biocytin in the NIC disclose a strong contingent of fibers that cross to the opposite side with the posterior commissure (PC) to terminate in the contralateral oculomotor and trochlear nuclei (114) as well as the NIC.

To examine what are the signals that NIC cells send to the oculomotor complex, output fibers of the NIC were studied intraaxonally in alert monkeys and then injected with a tracer (either horseradish peroxidase or biocytin) and studied light-microscopically after proper histochemical processing of the brain (115). Figure 5 illustrates the discharge pattern of one such neuron. It displays a burst-tonic discharge pattern, with tonic intersaccadic activity, pauses for upward saccades, and bursts before downward saccades (latency: 5.74 ± 4.4 ms, mean ± S.D.). A plot of the same cell's mean firing rate (figure 6A, ordinate) versus mean intersaccadic vertical eye position (abscissa) demonstrates an excellent linear relationship between the two variables (r = 0.94). In contrast, the firing rate of this cell was weakly related with the mean horizontal position that the eyes occupied between saccades (right inset of figure 6A). To establish whether this neuron belongs to the "regularly" or the "irregularly" discharging class of NIC cells (54), the coefficient of variation of interspike intervals (CV = SD/mean) was computed for different intersaccadic intervals (115). As shown in the left inset of figure 6A, the SD of this neuron's interspike intervals increased in proportion to the mean interspike interval. Its C.V. was equal to 0.04 at primary position which indicates that it is a regularly discharging cell. Parameters of the same neuron's bursts were also related to parameters of saccades. Figure 6B illustrates the excellent linear relationship (r = 0.88) between the number of spikes in the burst and the size of the downward component of saccades. No relationship was found between the number of spikes in the burst and the size of the horizontal component of saccades (inset of figure 6B). An excellent correlation (0.94) was also found between the duration of its bursts and the duration of saccades (figure 6C). Finally, an excellent correlation (r=0.97) was found between its firing rate and the vertical velocity of the eyes during smooth pursuit (figure 6D).

A camera lucida reconstruction of the same cell is illustrated in figure 7. The axon emerged from a small soma in the NIC and run caudally to decussate with the posterior commissure. It then run ventrally around the edge of the periaqueductal gray (PAG) to enter the contralateral NIC where it ramified into preterminal branches before continuing towards the contralateral oculomotor nucleus. The fact that terminal fields in the contralateral NIC, as well as the oculomotor and trochlear nuclei virtually disappeared when the posterior commissure was lesioned before a biocytin injection in the NIC, indicates that the posterior commissure could be the conduit of most of the NIC output to these nuclei (114). The integrity of these fibers is necessary for normal velocity to position integration in the vertical plane, as demonstrated by the fact that inactivation of the posterior commissure disabled vertical gaze holding, and advanced the phase while reducing the gain of the vertical VOR in the dark (116).

The notion that the horizontal neural integrator projects to horizontal extraocular motoneurons (#6, figure 4) is also supported by considerable evidence. A projection of the NPH to the abducens nucleus has been demonstrated with the help of both retrograde (117, 118) and anterograde (97, 94) bulk tracer injection techniques in the cat as well as in the monkey (95). It is also supported by the demonstration that feline neurons of the rostral NPH, which reliably encode horizontal eye position and/or display type II responses to vestibular stimulation, have been backfired from the abducens nucleus in the cat; typical latencies of antidromic responses are 0.23 ± 0.04 ms (68) for the former and about 0.6 ms (119) for the latter. Field potentials recorded in the abducens nucleus and triggered by spikes of position-velocity cells of the ipsilateral (contralateral) NPH nucleus are consistent with a small distal excitatory (inhibitory) connection (120). When the spikes of these cells are used

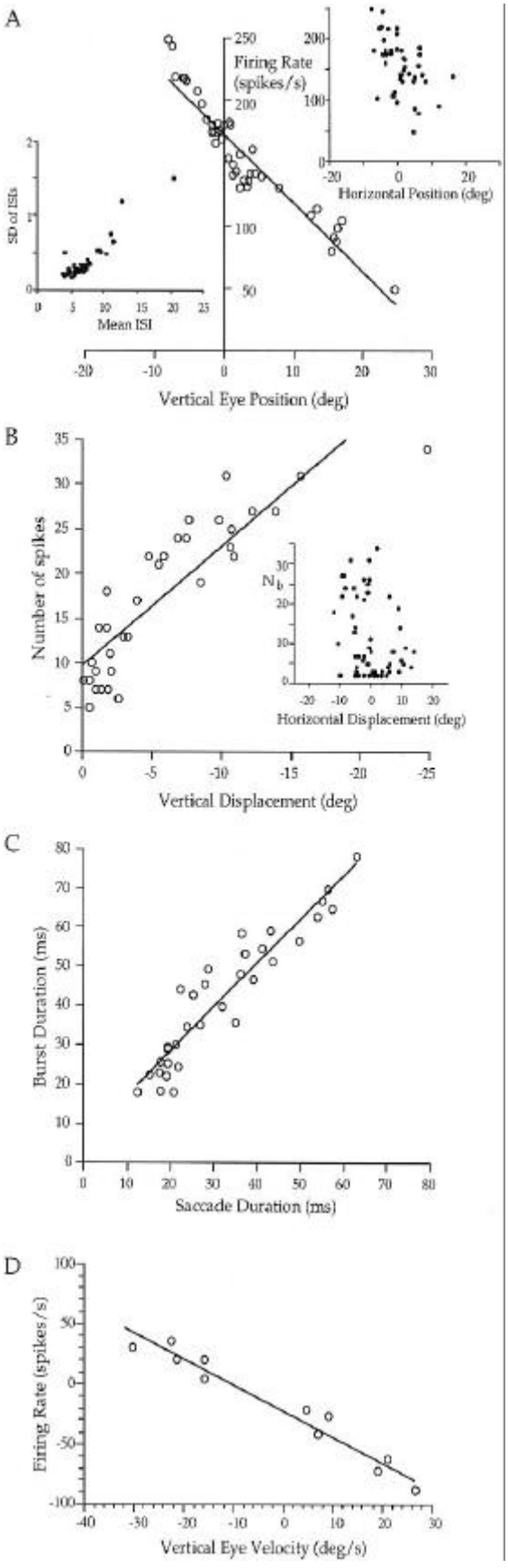

Figure 6. Quantitative analysis of the relationship between saccade metrics and the discharge pattern of the NIC neuron illustrated in figure 7 (modified from ref. 115, with permission). A) Plot of the mean intersaccadic firing rate (ordinate) versus mean intersaccadic vertical eye position (abscissa). Plots of firing rate (ordinate) versus mean intersaccadic horizontal eye position (abscissa) and S.D. (ordinate) versus mean (abscissa) of interspike intervals (ISI) are illustrated as insets (right and left, respectively). B) Plot of the number of spikes in the burst (ordinate) versus size of the downward component of saccades (abscissa). A plot of the number of spikes in the burst (ordinate) versus size of the horizontal component of saccades (abscissa) is illustrated as inset (solid circles). C) Plot of burst duration (ordinate) versus saccade duration (abscissa). D) Plot of firing rate (ordinate) versus smooth pursuit vertical eye velocity (abscissa).

as events to generate peri-event time histograms for physiologically identified abducens motoneurons, a monosynaptic (latency = 0.76 ± 0.05 ms; range 0.7 -0.9 ms) facilitation of the latter is revealed (68). Similar evidence supports the existence of an inhibitory connection between eye position encoding neurons of the rostral NPH and contralateral abducens motoneurons (68). Moreover, an inhibitory projection of NPH cells to the contralateral abducens nucleus is supported by the fact that injection of tritiated glycine (a putative inhibitory neurotransmitter that is taken up by the terminals which release it) is transported to the cell bodies they originate from in the contralateral NPH (121). Finally, it is supported by descriptions of the somatodendritic and proximal axonal morphology of NPH neurons following their intrasomatic injection with horseradish peroxidase (122, 94). With this means, three morphologically distinct classes of cells have so far been shown to inhabit the NPH: 1) Multidendritic cells of the caudal part of the nucleus with medium or large size somata and many dendrites with rich branches; their thick axons do not deploy recurrent collaterals and project to the cerebellum. 2) Principal cells of the rostral part of the nucleus with medium size somata and relatively few sparsely branched dendrites; their axons deploy terminal fields in one side of the brain stem (including the NPH). 3) Small cells of the dorsolateral NPH which issue recurrent collaterals and bilateral projections. Of the three, it is the principal cells that have been shown to distribute terminal fields within the abducens nucleus of the ipsilateral (or the contralateral) side of the brain (94) and could thus be output elements of the horizontal neural integrator. A camera lucida reconstruction of one such neuron is illustrated in figure 8.

Consistent with the vertical and oblique on-directions of some NPH neurons, an excitatory, monosynaptic projection of the NPH to trochlear motoneurons has been shown with intracellular recording methods. This projection survives chronic parasagittal cuts of the brain stem designed to interrupt the ipsilateral inhibitory projection of the superior and the contralateral excitatory projection of medial vestibular nucleus to the trochlear nucleus (123). An NPH projection to areas of the oculomotor complex that house vertical motoneurons has also been demonstrated with bulk tracer injection techniques (92).

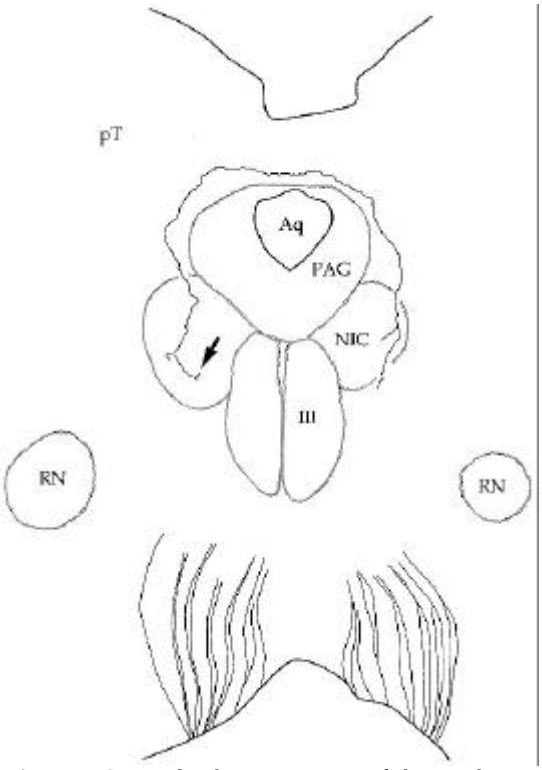

Figure 7. Camera lucida reconstruction of the initial several millimeters of the axonal system of an NIC neuron (modified from ref. 115, with permission). Abbreviations: III, oculomotor nucleus; Aq, aqueduct of Sylvius; NIC, interstitial nucleus of Cajal; PAG, periaqueductal grey matter; pT, pretectum; RN, red nucleus.

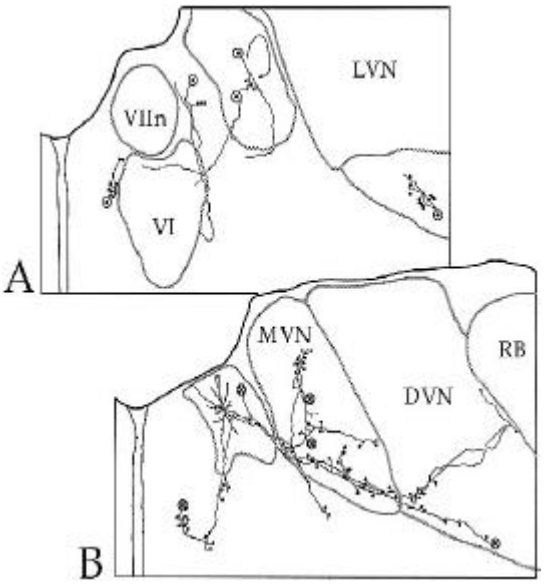

Figure 8. Camera lucida reconstruction of the initial several millimeters of the axonal system of a principal cell of the nucleus prepositus hypoglossi on two frontal sections through the brain stem with stereotaxic coordinates P 6.0 (A) and P 7.5 (B), respectively (modified from ref. 94, with permission). Stippled lines indicate borders of nuclei. Crosses surrounded by circles indicate points where the axon assumes a rostral trajectory. Abbreviations: VI, abducens nucleus; VIIn, facial nerve; DVN, descending vestibular nucleus; LVN, lateral vestibular nucleus; MVN, medial vestibular nucleus; RB, restiform body.

5.5. Motoneuronal projections of secondary vestibular neurons

The pattern of projections of secondary vestibular neurons onto motoneurons (#7 and #9 of figure 4, for vertical and horizontal neurons, respectively) depends on the input they receive from the peripheral end-organ and the nucleus that houses the cell bodies they originate from. Cells of the medial vestibular nucleus which respond to stimulation of the posterior canal project to the contralateral superior oblique and inferior rectus subdivisions of the oculomotor complex in both the rabbit and the cat (124). On the other hand, cells of the superior vestibular nucleus which respond to stimulation of the posterior canal project to the ipsilateral superior rectus and inferior oblique subdivisions of the oculomotor complex in the cat (124). In addition, cells which respond to stimulation of the anterior canal project to the contralateral superior rectus and inferior oblique (cells of the medial vestibular nucleus) or to the ipsilateral superior oblique and inferior rectus (cells of the superior vestibular nucleus) subdivisions of the oculomotor nucleus (125). The cells of the medial vestibular nucleus that participate in these projections are excitatory as indicated by the polarity of averages of field potentials recorded in the oculomotor complex and triggered from spikes of vestibular cells (126). In the horizontal system, neurons of the medial vestibular nucleus supply the ipsilateral (inhibitory cells) or the contralateral (excitatory cells) abducens and prepositus nuclei. This pattern of projections is consistent with the disynaptic EPSPs (IPSPs) that have been recorded from abducens motoneurons in response to stimulation of the contralateral (ipsilateral) vestibular nerve and the monosynaptic EPSPs (IPSPs) recorded from the same cells in response to the electrical stimulation of the contralateral (ipsilateral) medial vestibular nucleus (127). It is also consistent with averages of field potentials recorded in the abducens nucleus that were triggered from spikes of physiologically identified medial vestibular nucleus cells (antidromic latency equals 0.2 ms ± 0.05 for ipsilateral cells and 0.37 ms ± 0.1 for contralateral cells; ref. 68). In addition, Type I horizontal secondary vestibular neurons course with the ipsilateral ascending tract of Dieters to terminate in the medial rectus subdivision of the oculomotor nucleus (128).

With the exception of the pure vestibular cells, axons arising from all other functional classes of vertical secondary vestibular neurons (cf. Section 4.3) ascend through the MLF at least till the level of the trochlear nucleus (69). Accordingly, it is important to ask which of them establish connections onto vertical extraocular motoneurons (#7, figure 4). Unfortunately, only the pattern of terminations of PVPs has been established with the help of intraaxonal tracer injections first in the monkey (129) and later in the cat (130, 131). The pattern of axonal terminations of upward primate PVPs is illustrated in figure 9. Inhibitory cells of the superior vestibular nucleus have been shown to project to the ipsilateral inferior rectus and superior oblique subdivisions of the ipsilateral oculomotor complex. Conversely, excitatory upward primate PVPs of the medial and ventrolateral vestibular nucleus have been shown to project to the superior rectus and inferior oblique subdivisions of the contralateral oculomotor

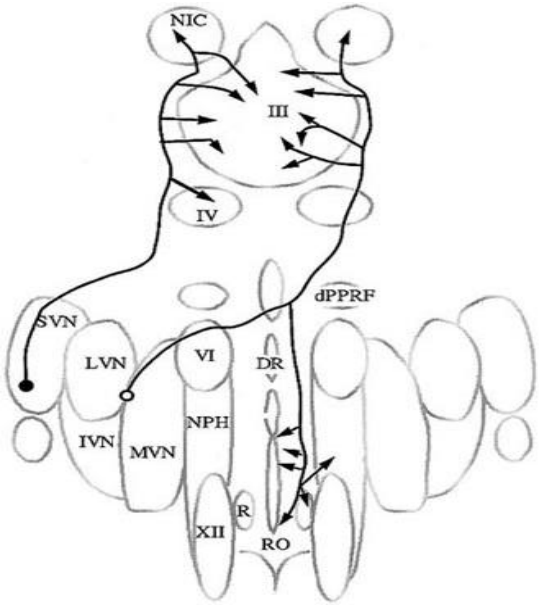

Figure 9. Schematic illustration of the axonal trajectories and projections (arrows) of one up PVP of the SVN (solid circle) and one up PVP of the MVN-VLVN (open circle; modified from ref. 129, with permission). Stippled lines are borders between nuclei. Abbreviations: IV, Trochlear nucleus; XII, hypoglossal nucleus; dPPRF, dorsal part of the paramedian pontine reticular formation; DR, caudal part of the dorsal raphe nucleus; IVN, inferior vestibular nucleus; NPH, nucleus prepositus hypoglossi; R, Rollers nucleus; RO, nucleus raphe obscurus; SVN, superior vestibular nucleus. Other abbreviations as in figures 7 and 8.

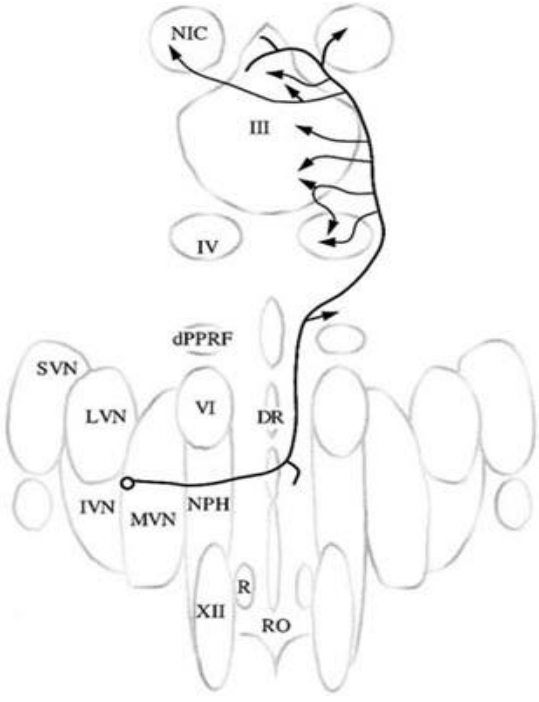

Figure 10. Schematic illustration of the axonal trajectory and projections of one down PVP of the MVN-VLVN (modified from ref. 129, with permission). Symbols and abbreviations as in figure 9.

nucleus. Excitatory downward PVPs (figure 10) have been shown to project to the inferior rectus and superior oblique subdivisions of the contralateral oculomotor complex. When averages of field potentials recorded in the oculomotor nucleus are triggered from spikes of feline downward position-vestibular neurons (DPV) excitatory monosynaptic responses are evoked in the contralateral inferior rectus and superior oblique subdivisions and inhibitory responses are evoked in the ipsilateral superior rectus subdivision of the oculomotor complex (131). When DVP axons were injected with a tracer, terminals were observed in either the inferior rectus and superior oblique subdivisions of the oculomotor complex contralateral to the soma they originate from or in the ipsilateral superior rectus and inferior oblique subdivisions (131). The importance of these fibers is shown by the fact that pontine MLF lesions (which interrupts the ascending projections of vertical secondary vestibular neurons) cause vertical gaze nystagmus (24).

As with the vertical system, of the several classes of functionally identified horizontal secondary vestibular nucleus neurons, it is the PVPs that have been shown to project to extraocular motoneurons with the help of intraaxonal tracer injections in the monkey (132). The pattern of axonal terminations of horizontal PVPs is illustrated in figure 11. In terms of vestibular responses, they are type I cells and they either project contralaterally to supply the abducens nucleus or they course with the ascending tract of Dieters to invade the ipsilateral subdivision of the oculomotor complex. McCrea and his colleagues were also successful in recovering BP units of the MVN projecting to the ipsilateral abducens and prepositus nuclei (132). A schematic illustration of the pattern of axonal projections of one such cell is illustrated in figure 12. Although their vestibular responsiveness is uncertain, these cells increase their discharge for ipsiversive abduction of the eyes; they are thus unlikely to correspond to the still elusive neuron that implements the inhibitory middle leg of the horizontal VOR. The fact that the primary vestibular projection to horizontal extraocular motoneurons is the excitatory one between the PVPs and the contralateral abducens motoneurons was demonstrated when averages of lateral rectus EMG were triggered from spikes of functionally identified secondary vestibular neurons (79). A small participation of BP, P and EHV cells in the same projection and a small inhibitory projection arising from ipsilateral PVP and EHV cells was also demonstrated in the same study.

5.6. Coennections between the vestibular nuclei, the NIC and the NPH

Besides supplying extraocular motoneurons with an eye position signal, secondary vestibular neurons supply the neural integrators with head velocity signals. The output of the neural integrators signal is then conveyed back to secondary vestibular cells and forward to extraocular motoneurons. Accordingly, the neural integrators of the saccadic system would contribute to integration in the vestibular system. This is a reasonable notion considering the responsiveness of NIC and NPH cells to vestibular stimuli and the symptoms of vestibular disease that follow their lesion (cf. Section 3).

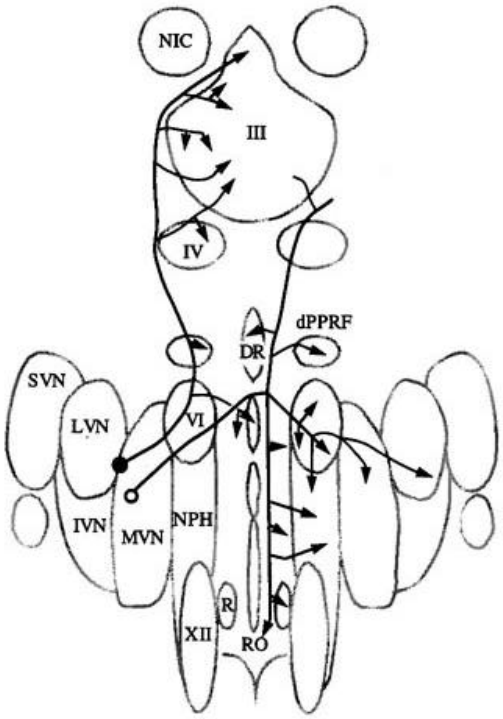

Figure 11. Schematic illustration of the axonal trajectory and terminations of one ipsilateral (solid circle) and one contralateral (open circle) horizontal PVP of the MVN-VLVN (modified from ref. 132, with permission). Symbols and abbreviations as in figure 9.

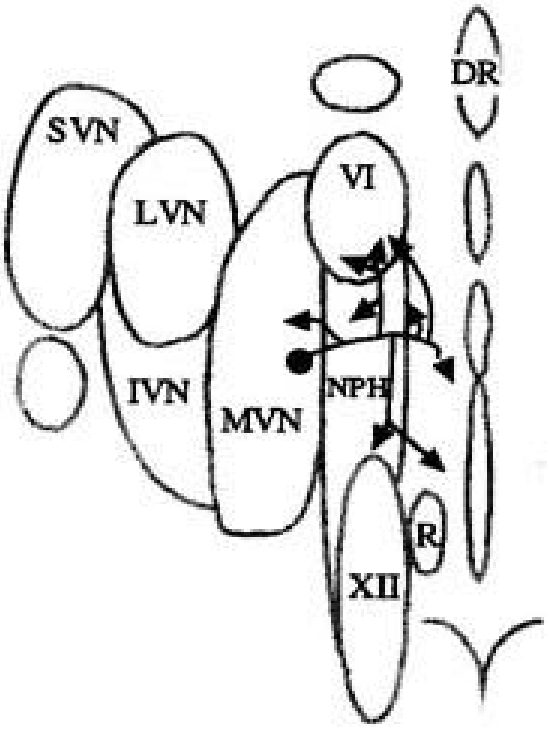

Figure 12. Schematic illustration of the axonal trajectory and terminations of an ipsilateral projecting horizontal burst-tonic cell of the MVN (modified from ref. 132, with permission). Symbols and abbreviations as in figure 9.

The place of different classes of cells in the hierarchy of neural events that underlie the process of integration in the vestibular system can be estimated from of a simple calculation: it concerns the phase difference between head acceleration (the input to the vestibular system) or eye position (the output of the system) and neuronal firing rate as a function of the frequency of stimulation. Plots of phase (and gain) against frequency (Bode plots) are an important ingredient of the analysis of linear time invariant systems. Besides, they are conceptually related to the first order differential equations that describe the discharge of oculomotor related cells (e.g., Eqs. 1-4). Take for example the last one which describes the discharge of extraocular motoneurons. Letting eye position (E) be a sine wave (sin(omega·t)), where omega is the frequency of rotation in radians per second, t is time, and omega·t = fi (the phase difference between eye position and neuronal firing rate), then substituting into Eq. 4 and solving for fi when $F_R = F_0$, demonstrates that $fi = \tan^{-1}(omega \cdot r/k)$, where k and r have the usual meaning of neuronal position and velocity sensitivity. The phase difference (fi) between eye position and firing rate can be determined experimentally. This has been done for several frequencies and classes of oculomotor related cells (tables 1-3 and 5). For the sake of simplicity, I will concentrate on one frequency of rotation (roughly 0.2 Hz) which has been employed by several workers.

Starting with the input side of the system, the discharge of feline secondary vestibular neurons leads the sinusoidally modulated eye position by about 100 deg in horizontal cells (133, 68) and about 70 deg in vertical cells (134, 130). In contrast, the discharge of extraocular motoneurons is almost in phase with eye position (cf. table 5). It is this phase shift that is contributed by the neurons that comprise the neural velocity to position integrators. The phase difference between their discharge and eye position is summarized in tables 1 and 2. Estimates range between 10 - 60 deg of phase lead re eye position for NPH cells (cf. table 2) and about 40 deg for burst-tonic and irregular-tonic cells of the primate NIC (54). It must be noted that the vestibular modulation of the discharge of NPH BT and T cells and NIC BT cells must be related to the vertical eye movements they cause rather than the vestibular signals they receive, because it does not occur during VOR suppression (54, 64).

The fact that the NIC and the NPH can influence the response properties of vestibular nuclear cells and the VOR while NIC and NPH cells respond to vestibular stimuli would lead one to suspect the existence of reciprocal connections between the NIC the NPH and the vestibular nuclei. Indeed, NIC cells receive input from secondary vestibular nucleus neurons as indicated by the fact that they are di-synaptically excited from the contralateral vestibular nerve, in both the cat and the monkey (135, 136). There is some controversy concerning the signals carried by and the functional identity of the thus affected NIC cells; it is thought to be head velocity (pitch) cells according to some authors (137) and position cells according to others (138).

However, this distinction is unlikely to be clear cut given the fact that there is no correlation between a neurons phase lead and its position sensitivity or CV (55).

Starting with the early reports of Muskens (139) and Lorente de N— (140), a projection from the vestibular nuclei to the NIC (#8, figure 4) has been consistently described over the past half century by many authors with the help of several techniques (reviewed in ref. 26). This projection primarily originates from the ipsilateral superior and the contralateral medial vestibular nucleus as demonstrated by the disclosure of retrogradely labelled cell bodies following biocytin injections in NIC (114). The projection that originates in the superior vestibular nucleus is inhibitory and the one that originates in the medial vestibular nucleus is excitatory as indicated by the fact that the electrical stimulation of these nuclei evokes monosynaptic IPSPs and EPSPs, respectively, in NIC neurons (141, 142, 136). Consistent with this, electrical stimulation of the labyrinth evokes disynaptic EPSPs in the contralateral NIC and disynaptic IPSPs in the ipsilateral NIC (136). Cells located in the contralateral medial and the ipsilateral superior vestibular nucleus which receive posterior canal information have been shown to project to the NIC in both the rabbit and the cat, on occasion bilaterally (124). Since as summarized in Section 4.3 secondary vestibular neurons are functionally diverse, it is important to ask which of them project to the NIC. So far it is vertical PVPs located in either side of the brain and thus corresponding to both excitatory and inhibitory cells, which have been shown to project to the NIC in both the cat (131) and the monkey (129), on occasion bilaterally.

Early anatomical descriptions of an NIC projection to the vestibular complex (#11, figure 4) were based on anterograde degeneration techniques in the cat (143, 108) and monkey (107), as well as the retrograde (74) and anterograde transport of tracers (144, 110). More recently, NIC projections to the vestibular nuclei (mainly the ipsilateral superior and medial vestibular nuclei) were demonstrated with injection of biocytin and PHAL in the NIC (114). The diameters of biocytin labelled NIC fibers that were traced to the vestibular nuclei (mean: 2.3 microns; SD: 1.1; N = 70) agree remarkably well with the conduction velocities of NIC cells that were antidromically activated from the MLF near the abducens nucleus (12 - 16 m/s; ref. 135). The projection of NIC neurons to the vestibular nuclei is excitatory (145). Yet, activation of NIC neurons inhibits type I neurons of the ipsilateral vestibular complex, presumably due to the excitatory influence they exert upon type II vestibular neurons (146). The importance of this projection is indicated by the fact that bilateral NIC lesions in the cat disrupt the responses of secondary vestibular neurons to head rotation. Thus, the depth of modulation (gain) of horizontal vestibular neurons decreases following lesions of the NIC but the amount of the phase by which their discharge lags head acceleration during sinusoidal vertical rotation remains unchanged (147). In contrast, the gain (re acceleration) of vertical secondary vestibular neurons decreases (mean±SD: 1.27±0.68 spikes/s/deg/s^2; range: 0.22 - 2.9 spikes/s/deg/s^2) by comparison to what is the case in normal cats (mean±SD:2.07±0.78 spikes/s/deg/s^2; range: 0.88 - 3.3 spikes/s/deg/s^2). Furthermore, the amount of the phase by which the discharge of vertical vestibular neurons lags head acceleration during sinusoidal vertical rotation of the head decreases by 30 deg following such lesions (26).

There is some information concerning the signals carried by (and the functional identity of) NIC cells that project to the vestibular nuclei. For example, NIC cells that encode down (but not up) eye position and are di-synaptically excited from the contralateral labyrinth have been backfired from the region of the ipsilateral medial vestibular nucleus (138). Additional information, largely rests on the physiological identification of NIC cells from the MLF at the level of the abducens nucleus. This applies to cells whose discharge is more deeply modulated by rotations in the plane of the vertical canals (134) as well as a few BT ones (3 of 25 tested; ref. 148). In contrast, interstitiospinal cells receive input preferentially from the horizontal canals (149).

NPH cells also receive input from secondary vestibular nucleus neurons (#10, figure 4) as indicated by the fact that they are di-synaptically excited from the contralateral vestibular nerve, and di-synaptically inhibited from the ipsilateral vestibular nerve in the cat (150). The vestibular projection to the primate NPH is provided by the type I (horizontal) PVPs as shown with the help of intraaxonal injection of tracer in functionally identified units (132). The vestibular responses of NPH cells are mainly type II (ipsiversive cells) but also type I (contraversive cells), in the cat (60) and mostly type I, in the monkey (64). The existence of a reciprocal projection of the NPH to vestibular nuclei (#12, figure 4) has also been demonstrated. These reciprocal connections are bilateral, concern several vestibular nuclei (medial, superior, descending and ventrolateral) and have been demonstrated with both retrograde (92, 95) and anterograde (151, 92, 95) techniques.

6. MODELS

Successful models of the neural integrators should capture the crucial biological facts that are known about them. These include the ability to produce eye position signals from eye velocity signals which often ride on a steady background discharge (cf. Section 4), the properties of eye movements which result from lesions of its elements (e.g., drifts with realistic time constants, multiple resting points; cf. Section 3), as well as the qualitative (e.g., burst-tonic or tonic) and quantitative (e.g., the range of values of the parameters F_0, k and r) properties of discharge of its constituent elements (cf. Section 4). Here, I briefly describe existing models of the neural integrators and examine their ability to explain how a piece of neural tissue can engage in Newtonian calculus.

With few exceptions, existing models of the neural integrators make use of some form of positive feedback. In its first and simplest form this arrangement was proposed by Kamath and Keller (1976). These authors assumed that the neural integrator is made of a

pool of neurons each one of which is described by an equation of the form,

$$y(t) + tau \cdot \dot{y}(t) = x(t) \quad (5)$$

where x(t) is the input that the cell receives, y(t) its output and tau its time constant (5 ms; ref. 152). In the absence of positive feedback, a neural integrator composed of such cells would have a time constant of 5 ms. In the presence of positive feedback (of gain k) Eq. 5 becomes,

$$y(t) + tau \cdot \dot{y}(t) = x(t) + k \cdot x(t) \quad (6)$$

The gain of the closed loop system described by Eq. 6 is,

$$\frac{y(s)}{x(s)} = \frac{1/tau}{s + 1/T} \quad (7)$$

where s is the Laplace variable and T (the time constant of the system) is equal to tau/(1-k). For the neural integrator to have a time constant of 20 s when tau = 5 ms, k must equal 0.99975. The limitations of this model (shared by several subsequent ones) were recognized early on. Firstly, as documented in Sections 4 and 5, cells feeding into the neural integrator can have relatively high background discharges which would be integrated together with their modulated component (the transient velocity signal). This problem is not important when the integrator input originates in MLBs (these emit bursts for saccades but otherwise they are silent). It becomes serious when considering other sources of integrator input (e.g., vestibular cells; cf. table 3). Secondly, these models are not robust because they are very sensitive to small changes of their feedback gain. For example, a value of k 10% less than ideal results in an integrator time constant of 50 ms. Finally, unlike most of the units encountered in the NIC and the NPH (cf. Section 4), signals carried by model units are modulated in concert with eye position and not eye velocity. Conceivably, the tonic (P) neurons of the NIC and NPH could distribute the output of the neural integrators while velocity cells are limited to computational stages closer to the input (60). Consistent with this idea, Escudero and his colleagues (68) demonstrated that tonic NPH cells project to the abducens nucleus more frequently than burst-tonic NPH cells. However, even if this result reflects the true organization of the NPH and not a sampling bias, it does not hold for the NIC where burst-tonic cells have been shown to project to extraocular motoneurons (cf. Section 5).

To address these shortcomings, a series of models were proposed by Robinson and his colleagues (153, 154, 155). The first one (153) achieves positive feedback by means of a lateral inhibitory network of homogeneous neurons which is driven by a pair of push-pull velocity inputs. Due to the distributed nature of the feedback connections, the strength of any one of these need not be precisely controlled. Further, the model manages to integrate just the time varying part of the input signal and not its time invariant part. However, the output of this model has the same sign as the feedback employed (negative). Therefore, the position related modulation of the discharge of motoneurons must rely on some form of disinhibition. Further, the model replicates the discharge pattern of tonic units but not that of the burst-tonic units (the majority of NIC and NPH cells; cf. Section 4). A later incorporation of a second excitatory layer (154), allowed the model to integrate velocity inputs carried by fibers with different background discharges. It also allowed it to reproduce the discharge pattern of burst-tonic units and endowed it with excitatory as well as with inhibitory connections with motoneurons thus accounting for their bi-directional modulation. Consistent with the modular architecture of this model, the eye drift which follows NIC lesions in the monkey has multiple resting positions and is a sum of exponentials with fast and slow time courses instead of a simple exponential (23). But, this model can not reproduce the large variety of position and velocity sensitivities displayed by burst-tonic neurons encountered in the NIC and the NPH.

This drawback was remedied by the last model from this group (155) which also avoids the problem of explicitly setting up the weights of the connections between units. Instead, the network learns these weights slowly through a process that compares desired and executed movements and adjusts the weights of connections until a correct movement is executed. The units of this network replicate several burst-tonic discharge patterns encountered in the NIC and the NPH. Unfortunately, this model is not robust. Furthermore, because of its uniformly distributed connections, lesions in this model should cause a drift of eye position towards a unique resting point with a simple exponential time course. This is not what is seen in monkeys after lesions of the NIC (23).

A somewhat different model of the neural integrator uses two half-center integrators (located in opposite sides of the brain) and relies on commissural connections to provide its two halves with positive feedback (156). Probably the most convincing evidence to date in favor of this model has been obtained in the vertical system of the monkey; interruption of the PC of this species has been shown to cause gaze nystagmus (116). On the other hand, there is convincing evidence obtained in the horizontal system of the goldfish, that undermines the importance of commissural fibers in velocity to position integration. As described in Section 3, a hind brain nucleus of this species contains neurons firing in relation to eye position during spontaneous eye movements and sinusoidal head rotation (nucleus I). Its bilateral inactivation causes integrator failure in the same species, while interruption of the midbrain commissures through midline sagittal cuts does not (46). Accordingly, these authors suggested that integration is largely due to the inherent electroresponsive properties of relevant cells (46).

Along similar lines, a model that relies on short term potentiation to adjust the time course of the synaptic transmission between integrator input and integrator cells has been proposed (157). This model needs some more work to replicate the discharge pattern of integrator cells that do not burst for saccades (the various classes of tonic cells described in Section 4) as well as the bi-directional modulation of all integrator cells. However, its major drawback is the absence of any evidence to indicate that synaptic potentiation is

necessary for velocity to position integration. If this is shown to be the case, and if the time course of the synaptic potentiation is long (equal to the time constant of the integrator) no additional mechanisms are needed. Since in this case integration is achieved on a single cell basis, the loss of individual neurons would not compromise the integrator. On the other hand, if the time course of the synaptic potentiation is shown to be small (a few hundred milliseconds) this model can serve as the front end of an integrator model that also relies on positive feedback loops to function properly. A model of the neural integrators that relies on units such as these was recently proposed (158).

All in all, no model specific enough to withstand a comparison with biology can replicate all of the salient features of neural velocity to position integration. On the other hand, it is fair to say that several crucial properties of the neural integrators have been replicated by some existing model. To pass a first verisimilitude test, future models of the neural integrators will have to demonstrate global consistency in a potentially eclectic combination of features from many existing models.

7. CONCLUSIONS

A wealth of information is available to indicate that the neural velocity to position integrators are largely confined to three heavily interconnected brain stem structures: 1) The nucleus prepositus hypoglossi, 2) The vestibular nuclei and 3) The interstitial nucleus of Cajal. The first two are largely responsible for integration in the horizontal plane while integration in the vertical plane is largely accomplished by the latter two. Cells encountered in these regions display a more or less intense phasic signal related to saccades and a tonic signal related to eye position. Depending on the relationship between their rate of discharge and the position of the eyes, these cells have been subdivided into regular or irregular, high-threshold or low threshold, and sensitive or insensitive to position and/or velocity. Several models have been proposed in an effort to capture the salient biological features of neural integration. Although, no model can replicate all of them, it is fair to say that several crucial properties of the neural integrators have been replicated by an existing model or another. Eclectic combination of features from many proposed models could permit the construction of more realistic models of the neural integrators in the near future.

8. ACKNOWLEDGEMENTS

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