Vestibular signal processing by separate sets of neuronal filters

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Abstract. Second-order vestibular neurons (2\textdegree VN) are the central element for the transformation of body motion-related sensory signals into extraocular motor commands for retinal image stabilization during locomotion. The wide range of motion dynamics necessitates sensory signal transformation in parallel, frequency-tuned channels. Accordingly, in various vertebrates, 2\textdegree VN have been shown to form differently tuned functional subgroups. In frog, these neurons subdivide into two separate populations with distinctly different intrinsic membrane properties, discharge dynamics and synaptic response characteristics. Frog tonic 2\textdegree VN exhibit low-pass filter characteristics and membrane properties that cause amplification of synaptic inputs, whereas phasic 2\textdegree VN form band-pass filters that allow frequency-dependent shunting of repetitive inputs. The differential, yet complementary membrane properties render tonic 2\textdegree VN particularly suitable for synaptic integration and phasic 2\textdegree VN for differentiation and event detection. Differential insertion of the two cell types into local circuits reinforces the functional consequences of the intrinsic membrane properties, respectively. As a consequence, the synergy of cellular and network properties creates sets of neuronal elements with particular filter characteristics that form flexible, frequency-tuned components for optimal transformation of all dynamic aspects of body motion-related multisensory signals.

Keywords: Membrane properties, low-pass filter, high-pass filter, semicircular canal, macula organ, vestibulo-ocular reflex, potassium conductances

1. Introduction

The relatively low temporal resolution of visual perception in vertebrates limits the ability to detect details in the surrounding world, particularly during high-speed locomotion on uneven surfaces that cause considerable head oscillations. Retinal image stabilization however allows accurate perception of the visual world independent of locomotor performance or dynamics. Image displacements and resultant degradation of visual information processing during self-generated body motion are compensated by counteracting eye and/or head-adjustments that are considered to derive from the sensory-motor transformation of vestibular, optokinetic and neck proprioceptive feed-back signals [1,2]. These sensory feed-back-driven reflexes act synergistically and stabilize retinal images even during high-speed locomotion. However, each of these sensory systems contributes to the generation of this motor behavior in a particular frequency range that is determined by the temporal resolution of the sensors for detecting image motion (visual), head motion in space (vestibular) or relative to the body (neck proprioception). The convergence of self-motion-related sensory signals in brainstem vestibular neurons indicates that central vestibular and subsequent higher-order nuclei form a multisensory system [1]. The convergence of different body motion-related sensory signals on self-motion detecting neuronal elements at various levels

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of the central nervous system is essential to cover the large range of motion dynamics but also to distinguish between e.g. tilt and linear translation [3] or between self-motion and passive body movements [21].

Vestibular sensory signals play a particular important role for the detection of motion-induced head movements and the generation of appropriate extraocular motor commands for compensatory eye movements [1, 62]. This is due to the considerable dynamic working range of this sensory system that detects changes in static head position via activation of sensory neurons in macula organs as well as high frequency/high acceleration head motion signals via activation of sensory neurons in the semicircular canals [62]. The large dynamic range of head movement-related sensory signals during locomotion, however, suggests that central sensory-motor transformation occurs in parallel frequency-tuned pathways [65] similar to the processing of visual [39,53], auditory [18], or somatosensory [33] signals. Consequently, this requires that the involved neuronal elements are not homogeneous but rather form subpopulations with distinct dynamic capabilities that are suitable to code and transform different dynamic aspects of self-motion-related neuronal activity. The implementation of this concept is facilitated by a transduction of the physical stimuli into neuronal signals by separate peripheral sensory elements and mediation to the central nervous system by dynamically adequate afferent nerve fibers.

2. Differential coding and mediation of vestibular sensory signals in dynamically adapted peripheral vestibular neuronal elements

In all vertebrates, hair cells in the sensory epithelia of semicircular canal and macula organs detect head acceleration and static changes of the head position relative to gravity. Deflection of the cilial bundle that protrudes from the apical surface of the hair cells into the endolymph-filled cavity of the labyrinth [30] transforms the inertia of the endolymph fluid in the semicircular canal and of the otoconia in the macula organs during head movements into graded electrical signals. These hair cells are morphologically heterogeneous (Fig. 1A) with respect to cell body, cilial bundle and synaptic structure of innervating afferent fibers [30]. Classification according to morphophysiological properties reveals preferential locations of particular subtypes in specific areas of the sensory epithelium (Fig. 1A) [30,36]. Specifically, length and shape of the kinocilium correlates with the epithelial position and physiology of a particular hair cell type (Fig. 1A) [7,8,30].

High input resistance, slow potassium currents, non-adapting responses to step-like bundle displacements, low-frequency sensitivity and low-pass filter-like cellular properties make extrastriolar hair cells in the macular epithelium particularly suitable for encoding static changes of the head position [7–9,30]. In contrast, low input resistances, particularly fast, resonating membrane currents responsible for marked response adaptation assign to hair cells along the macular striola high-pass filter-like properties, well suited for the coding of head acceleration [7–9]. Similar physiological differences were encountered for corresponding hair cell types in the semicircular canal cristae [30]. The organization of the vestibular sensory epithelia into more or less distinct regions of different hair cells types with interrelated morpho-physiological properties is excellently suited to decompose all aspects of body motion into neuronal signal components with different dynamics [30]. Even though, specific morpho-physiological characteristics differ between vertebrate groups (e.g. absence of bottle-shaped type I hair cells in amniotes), the classification of hair cells according to response dynamics and epithelial arrangement is highly conserved [62]. Moreover, preferential coding of different dynamic components by distinct hair cell types in the sensory periphery suggests that head motion-related signals are further processed in frequency-specific pathways [65].

Detection of specific temporal aspects of head motion (position, velocity, acceleration, jerk) and decomposition into respective neuronal signals by hair cells with adequate filter properties is only beneficial for further computation if the separation of the encoded signals in the sensory periphery is essentially retained during transmission to the central nervous systems. This requires dynamically matched connectivity of vestibular nerve afferents with the presynaptic hair cells. In fact, all semicircular canal and macula organs are connected to the brainstem by a large number of vestibular afferent fibers that differ from each other in several morphological aspects [30], such as cell diameter or transmitter content (Fig. 1B). As shown in frog, vestibular nerve afferents as a population form a continuum with respect to several properties (Fig. 1B,C). Specifically, thicker afferent nerve fibers have an irregular resting activity, a phasic discharge to step-like accelerations, large gains and small phase shifts (Fig. 1C) [32]. These fibers contact hair cells around the macular striola or
Fig. 1. Differential organization of morpho-physiological properties of frog vestibular hair cells and N.VIII afferent fibers. A. Spatially specific arrangement of morphologically different hair cells (type B, C, E, F) in the utricular macula; modified from [36,62]. B. Photomicrographs of consecutive semithin cross-sections illustrating glutamate- (Glu+) and glycine-immunopositive (Gly+) fibers in the N.VIII/N.VII; distribution of Glu+/Gly- and Glu+/Gly+ vestibular afferents with respect to fiber diameter; modified from [44]. C. Responses of anterior vertical semicircular canal afferent fibers to acceleration impulses (100°/s²; 100 ms); note that the response dynamics (phasic-tonic components) correlate with spontaneous discharge regularity (CV); modified from [32].

the central area of the canal crista [10]. In contrast, thinner afferent nerve fibers have a more regular resting activity, a tonic discharge to step-like accelerations (Fig. 1C), low gains and large phase shifts [32] and contact hair cells mainly in extrastriolar regions of the macular epithelium or the peripheral area of the canal crista [10,32]. Studies in frog have further shown that afferent fibers also differ in biochemical aspects such as co-localization and putative co-release of glutamate and glycine from the thickest afferents (Fig. 1B), potentially facilitating excitation of 2°VN through NMDA-type glutamate receptors [57,58]. In contrast, thinner afferents contain only glutamate and activate 2°VN through AMPA-type glutamate receptors [57,58]. Moreover, physiological specializations include differential distributions of ion channels as demonstrated for rodent vestibular ganglion cells [25,35]. The resulting difference in cellular conductance, and in particular potassium channel activation, might be the major determinant of discharge regularity and response dynamics that distinguishes the different types of vertebrate vestibular nerve afferents. In fact, comparison of known morpho-
physiological parameters in different vertebrate species suggests that apart from species-specific adaptations, hair cell/afferent fiber properties are evolutionary rather conserved [30].

The synaptic connectivity between a particular hair cell type and an afferent fiber with matched dynamic response properties suggests that decomposition of head motion dynamics by hair cells is largely maintained at the level of vestibular nerve afferents. Accordingly, the signal spectrum of afferent fibers ranges from long lasting continuous discharge in response to tonic head deviation to short bursts caused by high accelerations during rapid head turns as e.g. in frog vestibular afferents (Fig. 1C). To maintain the advantage of separate coding of different temporal aspects of head motion by vestibular nerve afferents, further processing in central circuits necessitates specific cellular vestibular elements that are equally heterogeneous in their intrinsic properties and signaling capabilities. Dynamically appropriate processing of the respective signals becomes even more demanding since vertebrate central vestibular neurons receive in part convergent inputs from other sensory systems such as the neck proprioception or the optokinetic system [1].

Frog central vestibular neurons (Fig. 2A) are a particularly good model for illustrating the cellular organization, since these neurons form subpopulations that express distinct intrinsic properties and form different, yet complimentary sets of neuronal filters throughout all vestibular subnuclei [13]. Moreover, intracellular recordings of vestibular neurons in an isolated frog brain preparation in vitro (Fig. 2B) allows identification as second-order neurons by labeled synaptic contacts of afferent fibers (Fig. 2A) or by monosynaptic EPSPs following separate electrical stimulation of ipsilateral vestibular nerve branches (Fig. 2C). Furthermore, these 2°VN can be classified based on cellular properties [63] and pharmacological manipulation within the framework of relatively intact central circuits reveals the nature of synaptic connectivity [62].

3. Differential organization of intrinsic membrane properties in frog central vestibular neurons

Frog 2°VN recorded in isolated in vitro whole brains distinctly separate into a larger subgroup of phasic (80%) and a smaller subgroup of tonic neurons...
Fig. 3. Functional characterization of frog 2°VN based on intrinsic membrane properties. A-D. Frog 2° VN subdivide into two distinct subtypes (phasic, tonic neurons) based on spike shape (A) and different aspects of the current-voltage relationship (B-D); phasic 2° VN (A1) have a single small after-hyperpolarization (AHP, single arrow); tonic 2° VN (A2) have a biphasic AHP with a fast, large (single arrow) and a delayed, smaller component (double arrow); insets in A2 show the biphasic AHP at extended time scales; open triangle and vertical dashed lines in A1,2 indicate spike threshold (at a voltage slope of 10 mV/ms); calibration bars in A1, B1 apply to A2, B2, respectively. Responses (upper traces) to series of hyper- and depolarizing current steps (lower traces) of a phasic (B1) and tonic 2° VN (B2); phasic but not tonic 2° VN exhibit an initial transient in response to positive current steps (open circle/square) that decreases to lower values during the plateau phase (closed circle/square).

C. Mean ± SD of the initial (open symbols) and plateau phase (closed symbols) of the current-voltage relationship of phasic (circles; n = 44) and tonic 2° VN (squares; n = 22).

D. Distribution of the ratio of early/late depolarization components in phasic and tonic 2° VN; an early transient is present in phasic (ratio > 1) but not in tonic neurons 2° VN (ratio ∼1); arrows and numbers indicate mean ± SD. Modified from [63].

(20%) [63]. The two non-overlapping types of vestibular neurons differ from each other in several interrelated intrinsic electrophysiological properties such as spike shape, current-voltage relationships, time constants and discharge properties (Figs 3–7). In particular, phasic 2° VN are characterized by action potentials with a monophasic after-hyperpolarization (AHP, Fig. 3A1), a rectifying I-V curve (Fig. 3B1,C) and a low input resistance [63]. The rectification of evoked voltage responses complies with a substantial impedance shunt during depolarization [13]. Moreover, injection of long positive current steps activate at pulse onset a high frequency burst of up to 3 spikes at a frequency of 150–200 Hz without subsequent sustained discharge (Fig. 4A,C), indicating a highly dynamic response profile of this neuronal subtype [13,63]. Since the transient activity in response to depolarizing current steps persists after blockade of synaptic transmission, a recurrent inhibition via inhibitory interneurons as a possible reason for the absence of a continuous discharge can be excluded [63]. Rather, particular dynamic membrane properties are the likely origin for the highly phasic responses.

Injections of ramp-like currents that cause voltage deflections above spike threshold fail to evoke a discharge in phasic 2° VN (** in Fig. 5A), unless the rate of rise of the depolarization exceeds ∼1.5 mV/ms [63]. Above this value, single spikes are activated (*** in...
Fig. 4. Different discharge dynamics of frog phasic and tonic 2°VN. A, B. A brief burst (A) and a continuous discharge (B) in response to injected long positive current steps (bottom traces) distinguish phasic (A) from tonic 2°VN (B). Insets in A show the initial burst at an extended time scale; calibration bars of the top trace in A, B and inset in A apply to all other traces in the same row, respectively. C. Firing rates of the phasic (open square) and the tonic 2°VN (open triangle and circle) as a function of current intensity. D. Firing rate of tonic 2°VN in response to positive current steps as a function of membrane depolarization; the dashed line indicates the average increase in spike rate (mean ± SD: 3.4 ± 1.9 spikes/s/mV). Modified from [63].

Fig. 5A), indicating that these neurons have both a spike threshold as well as a depolarization slope threshold (Fig. 5A). This behavior is generated by ionic conductances that cause fast rectification of the membrane potential during depolarization, prevent the activation of action potentials and thus act as a high-pass filter. In addition, the presence of a slope threshold for depolarization-evoked spike discharge indicates that these neurons are specifically suited to process afferent nerve signals of short duration [13,41]. The dominant current for this high-dynamic response characteristic is an I\(_D\) potassium channel, as evidenced from pharmacological experiments with low concentrations of 4-aminopyridine (4-AP) and confirmed by the presence of the respective channel protein (Kv1.1) in a specific group of central vestibular neurons [13]. Kv1.1 immuno-positive vestibular neurons are generally large and mainly located in the descending (DVN) and lateral vestibular nucleus (LVN; Fig. 5B), features that are compatible with the notion that phasic 2°VN are predominantly large projection neurons that target extraocular and spinal motoneurons [63].

The dynamic response characteristics of phasic 2°VN suggest that these neurons function as high- or band-pass filters for vestibular sensory inputs. Such filter properties become particularly evident during dynamic modulation of the membrane potential [13]. Injection of sinusoidally modulated currents at subthreshold levels for action potentials causes in phasic 2°VN a sinusoidal modulation of the membrane potential, that is characterized by a marked resonance at a stimulus frequency of \(\sim 15–40\) Hz (* in Fig. 6A\(_1\)) depending on the resting membrane potential [13]. Above spike threshold, action potentials are triggered around subthreshold impedance resonance frequency (Fig. 6A\(_2\)). Importantly, a spike discharge is absent at stimulus frequencies below \(\sim 10\) Hz in all phasic 2°VN. Above this lower limit, single spikes are triggered in synchrony with each depolarizing half wave of the voltage deflection up to a frequency of 80 Hz depending on the recorded neuron (Fig. 6A\(_3\)). The upper limit for faithful activation of action potentials during each cycle of the sinusoid depends on the resting membrane potential and can increase to values of > 100 Hz with depolariza-
Fig. 5. Functional characteristics and cellular basis of transient responses in phasic $2^\circ$ VN. A. Injections of ramp-like currents (lower gray traces) gradually depolarize the membrane potential above spike threshold without triggering action potentials (*), except when the slope of the depolarization exceeds $\sim$1.5 mV/ms (**); the inset in A shows responses and current ramps below (*) and above (**) slope threshold at an extended time scale. B. Cross-sections through the caudal hindbrain (level see inset in B$_1$) illustrating Kv1.1 potassium channel-immuno-positive neurons (B$_1$) in the dorsal (auditory) nucleus (DN), the descending (DVN) and lateral (LVN), but not the medial vestibular nucleus (MVN); higher magnification of labeled neurons in the DVN from an adjacent section (B$_2$). Images in B, adapted from [13].

tion. The subthreshold impedance resonance and the restricted dynamic range of spike discharge of phasic $2^\circ$VN during membrane potential modulation indicate that these neurons behave as band-pass filters. The specific filter properties are caused by the activation of a low-threshold, voltage-dependent $I_D$-type potassium conductance because application of 10 $\mu$M 4-AP flattens the subthreshold impedance resonance and broadens the frequency range of spike discharge [13].

Tonic $2^\circ$ VN differ from phasic $2^\circ$ VN in a number of electrophysiological features that assign to the former intrinsic membrane properties with rather low dynamics [63]. Particular characteristics of tonic $2^\circ$ VN include action potentials with a biphasic AHP (Fig. 3A$_2$), a higher input resistance and a fairly linear I-V curve (Fig. 3B$_2$,C). In addition, subthreshold responses evoked by positive current pulses lack the sharp initial transient typical for phasic 2VN (Fig. 3B$_{1,2}$,D) as well as the pronounced inward rectification (Fig. 3C) that shunts the responses of the latter cell type. Furthermore, tonic $2^\circ$ VN exhibit an impedance increase during depolarization [13]. Compatible with these properties, injection of long positive current steps in tonic $2^\circ$ VN evokes a continuous discharge (Fig. 4B) that consists of a brief high-frequency burst that rapidly adapts to a steady state with a rate that increases linearly up to $\sim$50 Hz with increasingly larger currents (Fig. 4C,D). The rather linear discharge properties of tonic $2^\circ$ VN were confirmed following injections of ramp-like currents (Fig. 7). After reaching spike threshold around $-56$ mV, these neurons discharge continuously with a slight adaptation of the firing rate during the subsequent current plateau that is particularly obvious when the slope of the injected current ramp becomes faster (Fig. 7A–C). The relatively linear current-firing rate relationship, specifically during slow changes in membrane potential suggests that these neurons are partic-
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Fig. 6. Subthreshold and discharge modulation of phasic and tonic 2° VN. A,B. Subthreshold responses (A1, B1) and spike discharge (A2, B2) evoked by injection of sinusoidally modulated currents that increase in frequency up to 100 Hz (lower traces) in a phasic (A) and a tonic 2° VN (B); typically, phasic 2° VN exhibit a subthreshold response resonance (in A1) and a frequency-restricted spike discharge at ∼ 40 Hz (A2), while subthreshold response amplitudes (B1) and evoked spike discharge (B2) in tonic 2° VN decrease with frequency. Firing rate of action potentials evoked by injection of sinusoidally modulated currents in 16 phasic (A3) and 7 tonic 2° VN (B3); phasic 2° VN show a cell-specific phase-locked discharge up to 80 Hz in some neurons (A3); tonic 2° VN exhibit a discharge that usually decreases with stimulus frequency, although a resonance occurs at ∼ 6 Hz in several neurons (B3); the gray dashed line in A3, B3 represents the frequency increase of the stimulus sinusoids with time. Calibration bars in A2 apply to B2.

4. Frog second-order vestibular neurons form complementary neuronal filters

Frog phasic and tonic 2° VN form two separate subgroups based on a number of different cellular properties. Both types receive sensory inputs from any one of the semicircular canal and macula organs and both types project to extraocular motor or spinal targets [63]. These results suggest that central vestibular projections are organized as frequency-tuned neuronal elements as are labyrinthine hair cells and vestibular nerve afferent fibers [65]. Observed differences in membrane properties and discharge behavior between frog tonic and phasic 2° VN are mainly caused by different sets of potassium channels that generate optimally tuned neuronal low-pass and band-pass filters [64,65]. The formation of separate, yet complementary neuronal filter elements with flexible working ranges that can be tuned and adjusted by membrane polarization (Fig. 8A,B) [13] is excellently suited for differential processing of all dynamic aspects of head-motion-related sensory signals. The different filter properties of the two subtypes are likely adjusted to the activity spectrum of the different...
labyrinthine nerve afferents [32]. Accordingly, frog phasic 2° VN should be tuned to the discharge pattern of thick diameter afferent fibers during head movements to detect high-dynamic response components while, tonic 2° VN should be adapted to the discharge of thin diameter fibers that transmit sensory signal components related to static head deviation.

The different intrinsic subthreshold membrane and discharge properties of frog phasic and tonic 2° VN suggest that synaptic inputs from vestibular nerve afferents are differently processed in the two subtypes. Experimental protocols with combined intracellular current pulse injections and activation of synaptic responses revealed that depolarization causes amplification of labyrinthine nerve afferent-evoked monosynaptic EPSPs in tonic 2° VN and a shunt of the respective signals in phasic 2° VN [13]. A similar differential processing occurs for synaptic inputs that were activated by short pulse trains, corroborating the notion that tonic 2° VN are more suited for integration of afferent signals and phasic 2° VN for differentiation and event detection. Mimicking spike discharge patterns of frog vestibular nerve afferents during natural stimulation [16] by applying sinusoidally modulated trains of single electrical pulses to individual semicircular canal nerve branches in an isolated brain preparation (Fig. 2B) revealed pronounced differences in the dynamics of the evoked postsynaptic signals in the two types of 2° VN [41]. Compound EPSPs in phasic 2° VN have a fast rise, an early peak and a substantial subsequent shunt of the response. At higher pulse stimulus intensities, only few spikes are activated between the first pulse and the respective subthreshold peak response where individual stimuli have a frequency of 40–50 Hz (Fig. 8C). In contrast, tonic 2° VN exhibit compound EPSPs following electrical pulse train stimulation that have a slower rise time and a rather linear relationship between stimulus waveform and evoked voltage deflection, indicated by aligned peaks of stimulus and compound response (Fig. 8D). The evoked discharge profile is largely linear, mirrors the waveform of the underlying membrane depolarization and follows stimulus frequencies of up to 10–15 Hz (Fig. 8D).

The contrast between the large peak advance of synaptic compound responses in phasic 2° VN and the aligned stimulus and response peaks in tonic 2° VN correlates well with the expected signal processing capacities based on the differences in intrinsic membrane properties between the two cell types. Moreover, the different signal processing demonstrates that the dynamics of the synaptically evoked discharge matches the intrinsic frequency tuning of the respective neuronal type (Fig. 8A-D). Thus, the intrinsic filter properties and in particular the bandwidth of response resonance determines a specific frequency range, respectively, at which synaptic inputs preferentially evoke action potentials (Fig. 8C,D). However, the complexity of vestibular feed-forward and feed-back network connectivity in vivo or under experimental conditions in isolated brain preparations likely contributes in addition to the signal processing. Accordingly, the dynamics of sensory-motor transformation in central vestibular neurons is determined by cellular filter elements but supplemented by the network connectivity [62]. Possible circuits that are involved in shaping synaptic responses include inhibitory cerebellar projections and
Fig. 8. Frog tonic and phasic 2°VN form dynamically flexible low-pass and band-pass filter elements. A,B. The working range of the filter characteristics of both neuronal subtypes shift to higher frequencies during depolarization of the membrane potential (B). C,D. Typical responses of a phasic (C) and a tonic 2°VN (D) to stimulation of the anterior vertical canal (AC) nerve with a sinusoidally modulated train of electrical pulses (0–70 Hz; dashed line in lower trace); note the different response waveforms and discharge dynamics of the two vestibular subtypes. Modified from [13].

interneurons in the ipsilateral vestibular nuclei [41,56, 59,60]. In fact, local tonic type vestibular interneurons mediate a semicircular canal nerve-specific disynaptic GABAergic and glycinergic inhibition that is superimposed on the vestibular nerve-evoked monosynaptic excitation in phasic but not in tonic frog 2°VN [15]. Such a differential insertion of phasic and tonic vestibular neurons in inhibitory networks illustrates that the response dynamics of individual 2°VN results from a co-adaptation of matched intrinsic membrane properties and emerging properties of the networks in which the respective neurons are embedded.

5. Differential response properties in second-order vestibular neurons as organizational feature for frequency-tuned pathways

The presence of functionally distinct subtypes of frog 2°VN matches the presence of dynamically different hair cells and vestibular nerve afferent fibers and suggests that head motion detection and processing occurs in frequency-tuned channels that separately encode sensory components such as position, velocity, acceleration and jerk [65]. Furthermore, the concept of separating head motion-related sensory signals into different temporal components by dynamically specific neuronal filter elements is repeated for the generation and mediation of motor commands for e.g. compensatory eye motion. In fact, extraocular motoneurons and eye muscles in frog form populations of morpho-physiologically different subtypes, respectively, that carry an equally wide spectrum of signal dynamics as the sensory elements [23,62]. Thus, sensory-motor transformation of vestibular signals into extraocular motor commands along the three-neuronal reflex arc appears to occur in distinct pathways starting by decomposition of head motion dynamics up to the movement of both eyes for appropriate image stabilization.

The presence of dynamically different neuronal filters at each synaptic level along the vestibulo-ocular reflex pathway is necessary but not sufficient for parallel signal processing. In addition, an interconnection of pre- and postsynaptic elements with matching signal-processing capacities is indispensable. Therefore, larger convergence of afferent signals with different dynamics should be absent. This is essentially the case on the sensory side of the vertebrate vestibular periphery between hair cells and vestibular nerve afferent fibers [30] and on the motor side between extracocular motoneurons and individual eye muscle fibers [17, 55]. However, labyrinthine inputs converging on central vestibular neurons appear to violate this principle. Even though, 2°VN form dynamically distinct subpopulations in frog as in other vertebrate species [64] and thus comply with a conceptual separation of signals.
according to frequency range, labyrinthine afferent inputs in individual 2°VN originate from a larger spectrum of vestibular nerve afferents in frog [60] as in monkey [29]. Convergence of evoked monosynaptic vestibular afferent EPSPs from a wider fiber spectrum thus appears to be rather common [62] and suggests mixing of signals related to different dynamic aspects of head motion in most 2°VN. However, a complete mixing of these signals occurs only if all monosynaptic inputs from dynamically different afferent fibers converge at electrotonically comparable postsynaptic sites and activate the same type of glutamate receptors. The extensive dendritic trees of 2°VN offer the possibility that afferents with signals related to particular head motion dynamics synapse at different somato-dendritic sites as shown in cat [47]. Recruitment of different glutamate receptor subtypes by thicker (irregular firing) and thinner (regular firing) vestibular nerve afferent fibers as e.g. in frog [57] add differences in postsynaptic time courses of particular vestibular afferent inputs. As a consequence, longer or shorter site-specific synaptic time constants and receptor subtype-mediated responses specify neuronal computations such as integration or differentiation of head motion related signals. The mathematical convertibility of position-velocity-acceleration components of head motion allows transformation of one modality into another by relatively simple calculations that can be implemented at the neuronal level. Thus, convergence of signals from a larger spectrum of afferent fiber types with different response dynamics onto individual 2°VN does not contradict an organization of the vertebrate VOR pathway into discrete frequency-tuned channels. It rather emphasizes the particular importance of understanding the filtering properties of individual compartments of 2°VN. Future studies should therefore address the correlation between afferent fiber types, location of synaptic terminations on particular somato-dendritic sites and time course of the activated responses. Accordingly, specific arrangements of synaptic inputs from semicircular canal and macula organs could also explain the considerable convergence of signals from the two types of vestibular endorgans in frog [61] that detect and code different modalities of head motion. Appropriate convergence and filtering properties would allow solving general perceptual ambiguities such as the problem of tilt versus translation [3]. The clear separation of frog 2°VN into distinct subtypes makes this animal model excellently suited to further study the cellular aspects of frequency-specific sensory-motor transformation of head motion signals. Since all other vertebrates are also confronted with the problem of transforming and coding a vast range of body motion dynamics, separate frequency-tuned pathways for vestibulo-motor signals might be a general feature of vestibular information processing.

6. Conserved functional organization of cellular vestibular properties in vertebrates

Separation of 2°VN into functional subtypes with different response dynamics appears to be a common feature also in other vertebrates [64]. The distinction of central vestibular neurons into tonic and kinetic neurons, initially described in cat in vivo [54] correlates well with the functional classification of 2°VN in vitro as type A and B medial vestibular nucleus (MVN) neurons (Fig. 9) in guinea pig [4,51,52], rat [34,46,66] and mouse [26] or chicken [31]. The latter two subtypes differ in several membrane conductances that cause different spike shapes, discharge dynamics and resonance bandwidths, respectively [45,51,52]. The intrinsic properties, however, assign to the two mammalian vestibular subtypes functional characteristics that are much less distinct than those that distinguish between frog tonic and phasic 2°VN [64]. Accordingly, it is still not entirely resolved if mammalian MVN neurons form two separate subgroups [11,34] as in frog or canonical endpoints of a functional continuum [24,40,49]. In fact, long-term modifications in neuronal classification of MVN neurons after unilateral labyrinthectomy in guinea pig [11,12] suggests that type A and B MVN neurons express some homeostatic plasticity that allows shifting the boundaries of the classification parameters between the two subtypes. Since the classification of the two subtypes is based on particular differences in potassium rather than sodium conductances [27,28], a possible reciprocal conversion might simply reflect an increase or decrease of specific conductances or calcium-buffering properties that are typical for type A and B MVN neurons, respectively [26, 64].

The recent use of transgenic mouse lines allowed distinguishing MVN neurons into EGFP (enhanced green fluorescent protein)-expressing GABAergic inhibitory neurons (GIN line) and into the yellow fluorescent protein-16-expressing glycineric and glutamatergic neurons (YFP-16 line) [5]. Based on different spike shape characteristics, GIN and YFP-16 neurons correlate in part with type A and type B MVN neurons, respectively [5]. This elegant new and in-
novative classification scheme facilitates further physiological dissection of vestibular neuronal filter function and interspecies comparison of intrinsic properties and network circuitry. Interpretation of neuronal contributions to vestibular circuit organization based on transgenic mouse lines suggests that an inhibitory feed-forward side-loop mediating its effect on type B MVN neurons in mouse originates from a subset of GABAergic type A-like neurons in the parvocellular part of the MVN that differ in their response properties from vestibulo-ocular projection neurons [5,27,50]. This is compatible with the observation that mouse type B MVN neurons are inserted in a prominent inhibitory GABA- and glycinergic network [20], which is very similar to the observed circuitry in frog, where local tonic \(2^\circ\) VN (functionally equivalent to type A MVN neurons) mediate a GABA- and glycinergic inhibition onto phasic \(2^\circ\) VN (functionally equivalent to type B MVN neurons) [15,41]. Further similarities include a predominant role of tonic \(2^\circ\) VN/GIN-neurons/type A MVN neurons in vestibular commissural signaling in both frog and mouse [5,38] and the contribution of all vestibular subtypes to projections to extraocular motor and spinal targets [4,64]. Thus, independent of specific physiological details, central vertebrate vestibular neurons appear to separate into functional phenotypes that likely are the cellular basis for differential synaptic processing as illustrated in frog [64].

A differential functional role of rodent type A and B MVN neurons in vestibular signal processing, similar to frog tonic and phasic \(2^\circ\) VN (Fig. 9) is further supported by different frequency-tuning of the two mammalian vestibular subtypes [11,12,45]. In particular, type A MVN neurons are characterized by a weak discharge resonance, while type B MVN neurons have a pronounced resonance that emphasizes rather non-linear properties of this neuronal subtype. This is further corroborated by substantial rebound firing after hyperpolarization in mouse glycineergic/glutamatergic YFP-16 vestibular neurons assuming a coincidence between the latter cell type and type B MVN neurons [5]. The functional difference between the two types of mammalian MVN neurons corroborates a general separation of vestibular neurons into discrete signaling streams [65] for mediation of lower-frequency, low and medium amplitude signals on one end (rodent type A MVN neurons; frog tonic \(2^\circ\) VN) and higher-frequency, high amplitude signals on the other (type B MVN neurons; frog phasic \(2^\circ\) VN). Accordingly, the different cell types might be the central elements of the presumed modifiable/non-modifiable or linear/non-linear vestibulo-motor signaling pathways suggested earlier [19,37,43]. However, vestibular elements in both circuits are likely connected with presynaptic afferent fibers through a frequency-independent synaptic transmission [6].

The specific intrinsic response dynamics of mammalian type A and B MVN neurons and their differences make these two subtypes functionally equivalent to frog tonic and phasic \(2^\circ\) VN (Fig. 9), even though the general tuning is shifted to higher dynamics in frog [13]. The major difference between central vestibular neurons in frog and rodents is the absence of pacemaker conductances in frog phasic \(2^\circ\) VN and the pres-
ence of a prominent voltage-dependent potassium con-
ductance in the latter neuronal type [13]. This latter
conductance is the origin of the rapid accommodation
and thus the main cause for the low or absent resting
discharge in phasic 2°VN in the isolated frog whole
brain. This contrasts with the marked spontaneous
discharge of vestibular neurons in isolated guinea pig
whole brains [4] or in rodent or chicken slice prepa-
ration [64]. In the absence of a pacemaker activity
in frog phasic 2°VN, repetitive firing thus depends on
constant synaptic input, largely from vestibular nerve
afferents which have a rather low resting activity of 1–
10 spikes/s [16,22]. The major reason for the observed
shift in dynamic properties of frog and guinea pig or
rodent central vestibular neurons (Fig. 9) might be cor-
related with the difference in locomotor dynamics of
the different species. The presence of highly phasic
vestibular nerve afferents [16,42] and central vestibular
neurons in frog [63] suggests that vestibular sensory-
motor transformation is tuned to higher dynamics. In
view of the general notion of frog behavior this ap-
ppears at first glance somewhat surprising but directly
matches the animals’ particular movement strategy that
usually consists of discontinuous sequences of brief,
rapid orienting movements, interrupted by long periods
of immobility [48]. For this strategy a motion detec-
tion system with particularly phasic neuronal elements
that serve as event detectors is well suited. In contrast,
animals like rodents are constantly moving and thus
experience continuous body/head movements. Such a
body motion pattern is best coded and processed by
neurons with a substantial resting rate that can be mod-
ulated over a larger dynamic range [14]. Therefore,
differences between vertebrates in the response dynam-
icsofnuronsinthevestibularnetworklikelyreflect
ecophysiological adaptations related to a particular lo-
comotor strategy that requires appropriate tuning to the
frequency-range normally experienced by the vestibu-
lar system in each species. However as a common
enumerator, this task is performed in all vertebrates
by separate sets of filter elements that are suitable to
process the broad spectrum of body motion-related sig-
als. Flexibility through adaptive plasticity allows ad-
quate tuning of these filter properties when locomotor
dynamics changes during ontogeny (e.g. metamorpho-
sis of amphibians) or during aging in all vertebrates
(reduction of motility).

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References

facets of a multimodal sense, Ann Rev Neurosci 31 (2008),
125–150.
ments: effects on visual acuity and navigation, Nat Rev Neu-
rosci 6 (2005), 966–976.
solve the tilttranslation ambiguity. Comparison of brainstem,
cerebellum, and thalamus, Ann NY Acad Sci 1164 (2009),
and P.P. Vidal, Central vestibular networks in the guinea-pig:
functional characterization in the isolated whole brain in vitro,
lines subdivide medial vestibular nucleus neurons into dis-
crete, neurochemically distinct populations, J Neurosci 27
Frequency-independent synaptic transmission supports a lin-
ear vestibular behavior, Neuron 60 (2008), 343–352.
cells in the bullfrog utriculus. II. Sensitivity and response
dynamics to hair bundle displacement, J Neurophysiol 71
(1994a), 685–705.
[8] R.A. Baird, Comparative transduction mechanisms of hair
cells in the bullfrog utriculus. I. Responses to intracellular
innervation patterns and response dynamics in the bullfrog
utriculus and lagena, Brain Res 369 (1986), 48–64.
of vestibular nerve afferents in the bullfrog utriculus, J Comp
Godaux, P.P. Vidal, L.E. Moore and N. Vibert, Long-term
plasticity of ipsilesional medial vestibular nucleus neurons
after unilateral labyrinthectomy, J Neurophysiol 90 (2003),
184–203.
[12] M. Beraneck, E. Idoux, A. Uno, P.P. Vidal, L.E. Moore and
N. Vibert, Unilateral labyrinthectomy modifies the membrane
properties of contralesional vestibular neurons, J Neurophysiol
[13] M. Beraneck, S. Pflanzelt, I. Vassias, M. Rohregger, N. Vibert,
P.P. Vidal, L.E. Moore and H. Straka, Differential intrinsic
response dynamics determine synaptic signal processing in
[14] M. Beraneck, J.L. McKee, M. Aleisa and K.E. Cullen, Asym-
metric recovery in cerebellar-deficient mice following uni-
lateral labyrinthectomy, J Neurophysiol 100 (2008), 945–958.
H. Straka, Differential inhibitory control of semicircular canal
nerve afferent-evoked inputs in second-order vestibular neu-
rons by glycinergic and GABAergic circuits, J Neurophysiol
99 (2008), 1758–1769.
of primary vestibular afferents in the frog, Exp Brain Res 25
(1976), 369–390.
[17] J.A. Buttner-Ennever, The extraocular motor nuclei: organiza-
tion and functional neuroanatomy, Prog Brain Res 151 (2005),
95–125.


