A reevaluation of the vestibulo-ocular reflex:

New ideas of its purpose, properties, neural substrate, and disorders

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Article abstract—Conventional views of the vestibulo-ocular reflex (VOR) have emphasized testing with caloric stimuli and by passively rotating patients at low frequencies in a chair. The properties of the VOR tested under these conditions differ from the performance of this reflex during the natural function for which it evolved—locomotion. Only the VOR (and not visually mediated eye movements) can cope with the high-frequency angular and linear perturbations of the head that occur during locomotion; this is achieved by generating eye movements at short latency (<16 msec). Interpretation of vestibular testing is enhanced by the realization that, although the di- and trisynaptic components of the VOR are essential for this short-latency response, the overall accuracy and plasticity of the VOR depend upon a distributed, parallel network of neurons involving the vestibular nuclei. Neurons in this network variously encode inputs from the labyrinthine semicircular canals and otoliths, as well as from the visual and somatosensory systems. The central vestibular pathways branch to contact vestibular cortex (for perception) and the spinal cord (for control of posture). Thus, the vestibular nuclei basically coordinate the stabilization of gaze and posture, and contribute to the perception of verticality and self-motion. Consequently, brainstem disorders that disrupt the VOR cause not just only nystagmus, but also instability of posture (eg, increased fore-aft sway in patients with downbeat nystagmus) and disturbance of spatial orientation (eg, tilt of the subjective visual vertical in Wallenberg's syndrome).

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Limitations of conventional methods for evaluating the vestibulo-ocular reflex. Clinicians' notions about the vestibulo-ocular reflex (VOR) have been largely fashioned by the two commonest settings in which they are called upon to test this reflex: in the investigation of the complaint of dizziness, and as part of the examination of the unconscious patient.[1,2] Often, the purpose of the VOR during natural activities is overlooked. The VOR generates eye rotations that compensate for head movements. Head movements include rotations and translations (linear displacements); we start by considering the VOR during head rotations and discuss responses to head translations later in this review. For the image of a distant object to remain upon the fovea of the retina during a head rotation, an equal but opposite eye rotation must be generated. When this perfect compensation is achieved, the gain of the response (eye movement/head movement) is 1.0. Most laboratory studies of the human VOR, however, report the gain of the reflex to be 0.75 or less (see Collewijn[3] for a review). This has led to the conviction that the VOR, on its own, cannot provide clear and stable vision during head movements.[3,4] What other mechanisms could contribute to the generation of eye rotations that compensate for head rotations? Such eye movements can be initiated by visual information, inputs from neck proprioception, and by the generation of eye movements that anticipate head movements.[1,2] How important are these other mechanisms for producing compensatory eye movements compared with the VOR? Compelling evidence for the indispensable role of the VOR in everyday life comes from reports of patients who have lost the function of their vestibular labyrinths.[5-7] Acutely, all head movements (even transmitted cardiac pulsations) impair vision and cause oscillopsia—illusory movement of the environment due to excessive slip of images upon the retina. Eventually, some abatement of these visual symptoms occurs while such patients are stationary, mainly due to enhancement of visual, cervical

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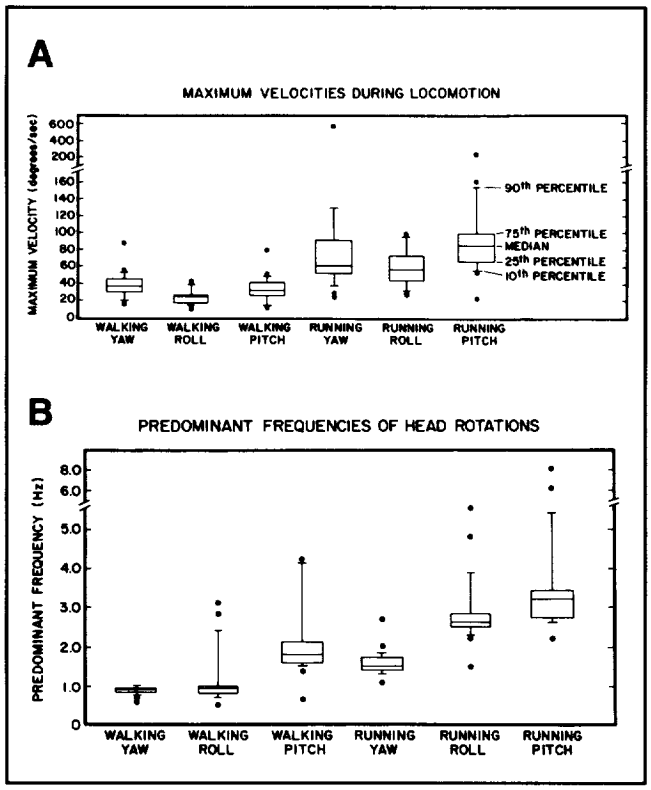


Figure 1. Summary of the ranges of (A) maximum velocity and (B) frequency of rotational head perturbations occurring during walking or running in place. Distribution of data from 20 normal subjects are graphed as Tukey box graphs, which show selected percentiles of the data. All values beyond the 10th and 90th percentiles are graphed individually as points. Note that peak head velocity typically does not exceed 150 deg/sec, but the predominant frequency may exceed 3 Hz, especially in the pitch plane. Reproduced from King et al.[12]

proprioceptive, and anticipatory mechanisms.[8-10] However, such patients continue to experience blurred vision *during locomotion*. In one of the first accounts of "Living without a balancing mechanism,"[5] an anonymous physician, J.C., reported: "During a walk I found too much motion in my visual picture of the surroundings to permit recognition of fine detail. I learned that I must stand still in order to read the lettering on a sign."

Thus, an important clue to understanding the normal role of the VOR is the nature of head movements that occur during locomotion. In this review, we first describe the characteristics of head movements that confront the VOR during locomotion, and then examine how well the VOR copes with them. Second, we address two aspects of the vestibulo-ocular responses that have only recently been examined: the torsional VOR and the otolith-ocular responses. Finally, we discuss recent ideas concerning the neural substrate of the VOR.

Characteristics of head movements during locomotion. Which characteristics of the head movements that occur during locomotion are so exacting that only the VOR can compensate for them? During locomotion, these are rotational head perturbations with predominant frequencies in the range of 0.5 to 5.0 Hz; the highest-frequency head rotations are in the pitch (vertical) plane (figure 1).[11,12] On the other hand, the peak velocity of these head movements generally does not exceed 150 deg/sec and, during walking, is usually less than 30 deg/sec, well within the range of operation of the VOR.[13] Thus, it is generally not the speed, but the *frequency*, of the head rotations during locomotion that presents the main threat to clear vision.

Loss of peripheral vestibular function leads to gaze instability and its visual consequences due to impairment of the VOR (see below). In addition, loss of vestibulo-spinal reflexes predisposes to head-trunk incoordination.[14] This raises the issue: how much does head instability in patients who have lost peripheral vestibular function contribute to their visual symptoms? Measurements of such patients' head rotations during walking or running in place do not show any increase of the angular velocity or frequency: they can stabilize their head during free walking as well as normal subjects.[6,7,15,16] Thus, the mechanical properties, due to neck muscle tone and the inertia of the cranium, prevent excessive vibrations of the head after the loss of vestibular sense. However, what *is* lost in these patients is the ability to sustain a steady angle of head orientation in the sagittal plane with respect to gravity (standard deviation of 3 degrees in normal subjects).[16] It has been hypothesized that this head orientation may be necessary to optimize the sensitivity of the otolithic organs of the labyrinth, which sense linear accelerations.[15,16] This finding, in turn, has suggested that the vestibular system works in a "top-down" fashion, with the brain paying particular attention to the orientation of the head in space rather than to the orientation of the trunk ("bottom-up," from feet to head) to which the head is "rigidly" attached. Such an organization is preferred in normal subjects and allows the head to serve as a "gaze-anchored" reference system. However, in patients who have lost vestibular sense, and in children learning to walk, a bottom-up control of posture may prevail, with a tendency to anchor head to trunk during locomotion.[16,17]

In summary, during locomotion, high-frequency head perturbations occur. Loss of vestibular function causes a variability of the angle of orientation of the head, but does not cause higher-frequency or higher-velocity head movements during locomotion, compared with normal subjects. Therefore, the visual symptoms reported by patients who have lost vestibular function are mainly due to gaze instability (due to loss of VOR) rather than head instability.

The properties of the VOR under natural conditions. Studies of the stability of gaze in normal

subjects during walking and running in place show that their gaze remains relatively stable, in contrast to patients with deficient vestibular function whose gaze instability leads to blurred vision and oscillopsia.[6,18] One important property of the VOR making it possible for the brain to generate eye movements to compensate for such high-frequency head rotations is its small latency of action—less than 16 msec.[19,20] This is much below the latency to onset of visually mediated eye movements such as smooth pursuit, the smallest values being about 75 msec.[21] Furthermore, the head perturbations that occur during locomotion are characterized by a randomness[18]; this property will limit the brain's ability to generate eye movements in anticipation of these head movements. Finally, the cervico-ocular reflex, which produces only small (ie, low gain) compensatory eye movements in normal subjects, makes a negligible contribution to gaze stability for the higher-frequency head rotations occurring during locomotion.

If the VOR is indispensable for stabilizing gaze and guaranteeing clear vision during locomotion, why do most studies of the human VOR report gain values of 0.75 or lower—values that would lead to visual symptoms such as reported by J.C.? Specifically, why is the gain of the VOR, in the horizontal and vertical planes during walking, typically 0.9 to 1.1,[18] 20% greater than values reported during the routine testing carried out in clinical laboratories? This discrepancy is probably due to the conditions of testing. A major factor is that the rotational stimuli applied in many reported studies of the VOR were at much lower frequencies than those occurring during locomotion. Furthermore, although caloric stimulation is invaluable for detecting unilateral labyrinthine dysfunction, it is also a low-frequency stimulus. Another factor, in many studies, is that subjects were rotated in darkness, an artificial condition that is known to reduce the gain of the VOR, even if the subject imagines a stationary target.[22,23] Thus, it seems that the VOR only performs at the level required to safeguard vision during test conditions that correspond to natural activities; at these higher frequencies of head rotations, other mechanisms that generate compensatory movements are comparatively inadequate. Why should the VOR "slouch" except when it is needed? What advantage could this provide?

Recent studies suggest that, during stationary or sedentary activities, we may not need a VOR. For example, vision is not appreciably impaired in patients with deficient vestibular function, compared with normal subjects, while they sit or stand stationary, and their gaze stability is similar to that in normal subjects.[6,7] In normal subjects, the gain of the VOR while at rest is approximately 0.75, but after the onset of a sudden (high-frequency) head rotation, rapidly rises to about 0.95.[24] Thus, gaze is perturbed at the onset of a sudden head rotation, but less so at the subsequent offset of rotation (figure 2). Humans may have a lower VOR gain while at rest because of the increased importance of performing fine motor tasks while stationary. The head perturbations that occur during locomotion require the gain of the VOR to be close to 1.0, but the rotations occurring during stationary activities do not pose such a threat to clear vision. During the latter, certain tasks entailing fine, continuous coordination of head, eyes, and hands actually require that the VOR be *negated*, and this may be more easily achieved if VOR gain is set at a lower level.

Thus, we propose that the VOR be tested using higher-frequency head rotations, something not easily achieved with older vestibular chairs. One technique that has been used to apply higher-frequencies stimuli is for the subject to actively generate head movements. Unfortunately, this technique also has limitations. Normal subjects can generate anticipatory eye movements to compensate for active head rotation,[25] and patients who lose vestibular function can use predictive mechanisms to generate compensatory eye movements.[8-10] As pointed out above, during locomotion, head rotations not only contain high-frequency components, but also have a randomness,[11,18] so such predictive mechanisms may be unable to compensate for an absent VOR. These findings raise questions about the reliability of studies using rotational stimuli applied in a predictable manner, especially active, self-generated head movements.[23,26] A more reliable, bedside method for testing the VOR is to apply passive, rapid head turns.[27] Patients are asked to fix upon a target while the examiner briskly turns their heads horizontally or vertically. The rotation need not be large, but should have a high acceleration and be unpredictable. If the VOR is working normally, gaze will be held steady, but, if not, a corrective saccade will be needed at the end of the head movement to refoveate the target.

In summary, it is not surprising that conventional vestibular testing sometimes fails to account for patients' symptoms during natural activities. The gain of the VOR depends upon the conditions of testing, especially the frequency of the stimulus. If we are to account for vestibular symptoms during natural activities, then it makes sense to test the VOR with stimuli that correspond to the head perturbations that occur during natural activities such as locomotion: rotations with a frequency range of 0.5 to 5.0 Hz, applied in a nonpredictable sequence. If transient head rotations are used, then a perturbation of gaze should be expected at the onset, but not the offset, of the stimulus (figure 2).

Properties of the VOR in the torsional plane. Head perturbations during locomotion have rotational and linear (translational) components in all three planes. This review has mainly concerned only horizontal and vertical rotations, but how well does the VOR compensate for the other components of the perturbations, in particular for head rotations in the frontal (torsional or roll) plane?

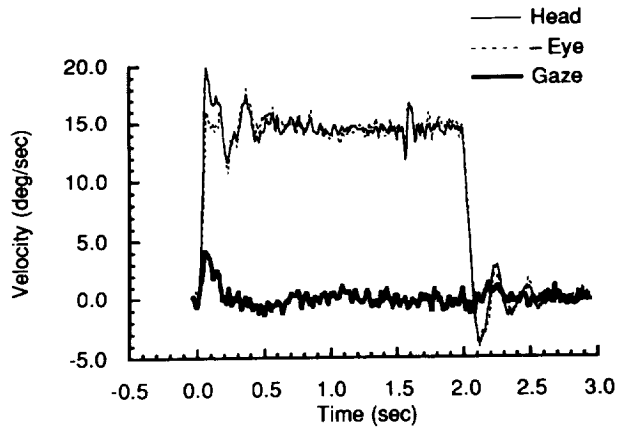
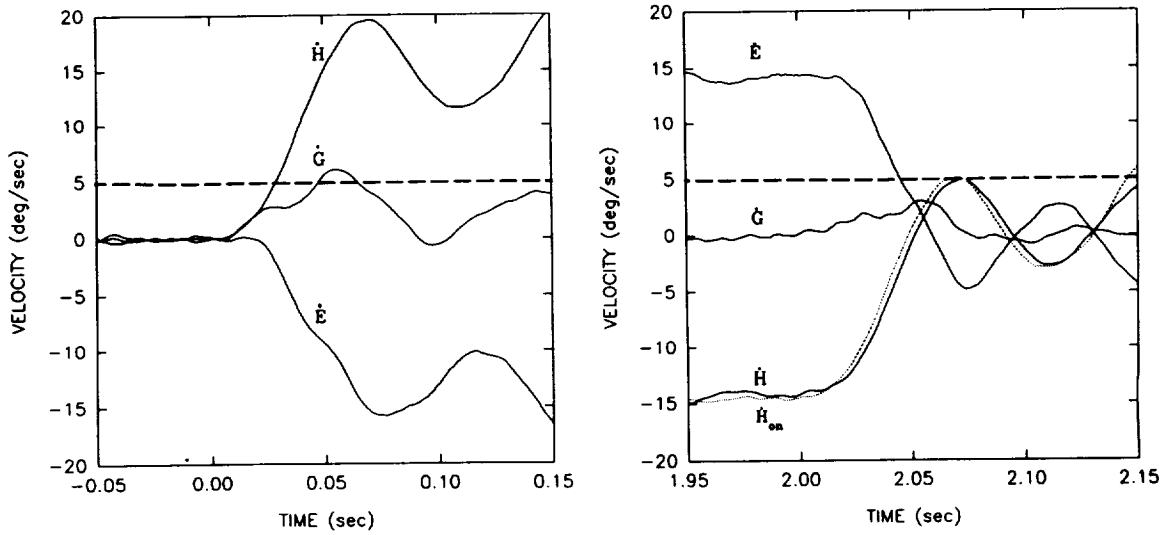


Figure 2. Typical example of visually enhanced VOR. Top left: complete response from a normal subject. Note that eye velocity is inverted (−Eye) to allow direct comparison with head velocity. Gaze velocity is perturbed more at onset than at offset of head rotation. Bottom: Comparison of onset (at left) and offset (at right) of two separate responses from the same subject, with both changes of head velocity occurring in the same direction. For purposes of comparison, the waveform of the onset head rotation (H_{on}, shown as a dashed line) has been transposed and replotted to compare it with the offset waveform (bottom right panel). Note that although the changes in head velocity at onset and offset have very similar magnitude and dynamic characteristics, gaze velocity is perturbed more than 5 deg/sec at onset, but not at offset. Time scales are different for top and bottom plots. Reproduced from Huebner et al.[24]



The VOR has different properties in the torsional plane compared with the horizontal and vertical planes.[28-31] Thus, the gain of the torsional VOR, under optimal circumstances, is never high enough to compensate for natural head movements (typically 0.65). Moreover, gaze stability[32] and the dynamic properties of the VOR during head rotations in roll differ, and the torsional optokinetic response is weak.[28] Why is this? First, head rotations in roll do not displace images from the fovea; only in the periphery of the retina (areas of sparser photoreceptor density) will there be an appreciable slip of images in the absence of compensatory eye movements. From a visual standpoint, a modest VOR is probably all that is required to lessen image slip in the periphery and maintain visual acuity. Second, perceptual mechanisms involved in the processing of visual information appear to be better suited for handling torsional disturbances than corresponding horizontal and vertical mechanisms. For example, certain torsional disparities are well tolerated by visual processing mechanisms[33-35] (eg, patients with Wallenberg's syndrome seldom complain of torsional diplopia), and the stability of torsional gaze, although much less constant than horizontal or vertical gaze,[32] does not appear to impair visual acuity or perception. In human subjects, a *static* head tilt (ear to shoulder) causes sustained conjugate counter-rolling of the eyes (ocular torsion) that is only about 10% of the head roll[28]; thus, the static ocular response does not compensate for the head tilt and may be vestigial (being more important in laterally eyed animals). Static counter-rolling may be due to the otolithic organs, and the feebleness of this response had suggested that the otolith-ocular reflexes are weak in humans. However, the otoliths do make substantial contributions to the stability of gaze under certain conditions (see below).

Disorders of the torsional VOR have received little attention, with the exception of the ocular tilt reaction (OTR), which consists of skew deviation, ocular torsion, and head tilt.[35-39] Such patients also show a deviation of the subjective visual vertical, although this does not correlate precisely with the amount of ocular torsion.[35] The OTR probably

reflects an imbalance of otolithic inputs, although an imbalance of posterior semicircular canal inputs may also contribute.[35] Thus, lesions affecting the vestibular labyrinth, vestibular nuclei, medial longitudinal fasciculus, or interstitial nucleus of Cajal[39] produce the OTR, which may be tonic (eg, in Wallenberg's syndrome) or paroxysmal (eg, in multiple sclerosis). Certain other brainstem disorders, such as syringobulbia, demyelination, vascular disease, and posterior fossa tumors may produce torsional nystagmus, which can be viewed as another type of imbalance of central vestibular connections.[40-42]

New views on the normal functions of the otoliths. Natural locomotion causes an optic flow of images upon the retina. As we traverse our environment, the rate of optic flow depends upon the proximity of objects, being greater for close objects.[43] Geometric factors suggest that when the fovea is directed towards a closely situated object the gain of the VOR must be increased to compensate for head rotations (due to head perturbations). This is because of the eccentric position of the eye in the head (this geometric fact means that pure head rotations cause translations, or linear displacements, of the eyes).[44-47] Furthermore, during locomotion, translations of the head occur (due to head perturbations and forward motion through the environment).[48-50] The component of the VOR that responds to head translations depends upon the otolithic organs, which is switched in when the subject views a near object.[47-49] This conceptualization has led to the development of new tests of otolithic function,[51-53] for example, comparison of the magnitude of eye movements during fixation of near and distant targets as the subject is translated laterally or fore-and-aft on a parallel swing (a swing with rigid vertical bars that prevents angular motion).[54] Another technique consists of placing the head of the subject in front of the axis of rotation of a vestibular chair; this achieves a combined angular-linear movement that stimulates both the semicircular canals and otoliths. The effect of otolith stimulation can also be measured during sustained rotation about an axis tilted from earth vertical (off-vertical axis rotation—OVAR), such as "barbecue-spit" rotation.[55-57] Such stimulation induces a continuous nystagmus, the slow phases of which have two components: a velocity drift of less than 10 deg/sec in the opposite direction to head rotation ("bias") and a superimposed sinusoidal modulation of slow phase velocity related to the angular velocity of rotation ("modulation"); normal ranges of responses have been defined.[57] Ultimately, as techniques permit, it will be necessary to measure the responses of the VOR to combined rotations and translations such as occur during natural locomotion. Conceptual schemes to account for the three-dimensional interactions of inputs from the semicircular canals, otoliths, and vision have been developed for the monkey[58] and humans.[59]

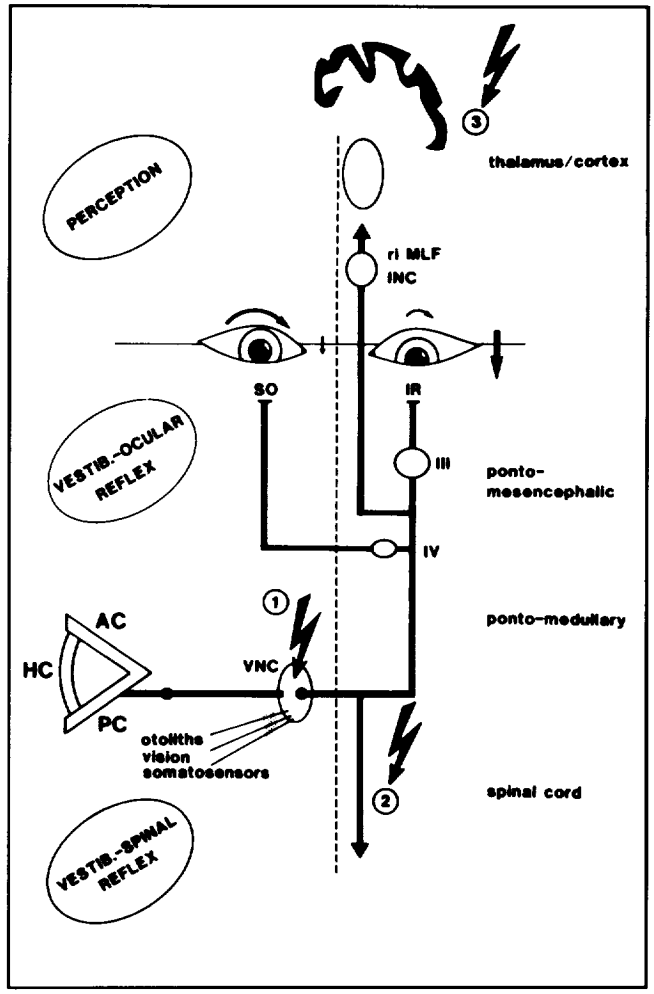


Figure 3. Schematic representations of the VOR. Elements that contribute to the overall, sensorimotor vestibular response. Inputs from the horizontal (HC), anterior (AC), and posterior (PC) semicircular canals converge with otolithic, visual, and somatosensory afferents in the vestibular nuclear complex (VNC). The outputs from the neural network in the VNC contact the extraocular muscles; here the principal three-neuron arc connections of the PC are shown passing to the trochlear (IV) and oculomotor nuclei (III) which contact the superior oblique and inferior rectus muscles. In addition, connections from the AC and PC contact the interstitial nucleus of Cajal (INC), which is important for eye-head coordination in roll and in vertical gaze holding, and to the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which is important in generating quick phases of vestibular nystagmus in the vertical and torsional planes. (Divergence or convergence of the vestibular nuclei network is not shown.) The VNC output (1) also projects to the spinal cord (2), to generate vestibulo-spinal reflexes, and to thalamus and cortex (3), to provide inputs for perception of movement. Thus, VOR pathways also mediate posture and perception.

The neural substrate of the VOR. The "elementary" VOR is a di- or trisynaptic reflex.[60] From the labyrinthine semicircular canals, primary vestibular afferents project to the vestibular nuclear complex (VNC) in the medulla (figure 3). From the

VNC, one or two interneurons project to the ocular motoneurons in the oculomotor, trochlear, and abducens nuclei (see Leigh and Zee[2] for a review of the anatomy). Although these oligosynaptic pathways are essential for the short-latency properties of the VOR, they represent only a portion of the connections subserving this reflex. Other pathways are needed to generate appropriately calibrated eye movements, to account, for example, for the proximity of the object of regard (otolithic and visual inputs) and to hold gaze steady at the end of the compensatory eye movement (gaze-holding or "neural integrator" function). Furthermore, primary vestibular inputs that serve the VOR send axon collaterals to neurons concerned with vestibulospinal reflexes and to cortical areas concerned with the perception of self-motion (figure 3).

Electrophysiologic studies of neurons in the VNC and adjacent structures, such as the nucleus prepositus hypoglossi, indicate that individual neurons will show varying combinations of signals encoding vestibular and other eye movement commands (such as quick phases) as well as visual and proprioceptive signals.[61-63] Such findings pose problems for conventional quantitative schemes of the VOR that assign "boxes" to represent specific properties of this reflex. On the other hand, recent attempts to represent the neuronal operations of the vestibular nuclei as a neural network capable of "learning" have been successful in simulating the diversity of responses recorded experimentally from these neurons.[64] For example, if the VOR is to compensate for head rotations in the vertical (pitch) plane, signals from the anterior and posterior semicircular canals must be transformed to produce appropriate contractions of the appropriate extraocular muscles—the vertical rectus and oblique muscles; this transformation is necessary since the coordinate frames of the canals and the muscles differ.[65] Experimental data indicate that the directions of head rotation for which neurons in the vestibular nucleus show their maximum response (sensitivity vector) vary widely and do not show any uniformity of alignment.[66] This finding suggests the convergence on these neurons of signals from different semicircular canals. When a three-layered neural network was successfully "trained" to solve the canal-muscle transformation problem, the sensitivity vectors of the middle layer of the network were widely dispersed, similar to those recorded experimentally.[65] This approach—distributed parallel processing of neuronal signals—has gained considerable popularity and shed a number of insights into the way that the brain makes its computations; for example, there is no unique solution to problems like the canal-muscle transformation, but the relative weighting between different synapses of the model is determined as the model "learns" to "solve the problem."[65] Further, the dynamic properties of the VOR of the newborn infant differ from those of adults; this maturation occurs during the first 2 months of life as visual information becomes available to provide the "error signal" necessary to train a network of neurons.[67]

Another important function performed by neurons in the medial vestibular nucleus and the adjacent nucleus prepositus hypoglossi is the gaze-holding or "neural integrator" function. Most ocular motor commands are encoded in terms of velocity, but a position component is also necessary to hold the eyeball in an eccentric position in the orbit against elastic forces that tend to return it to primary position. Destruction of the medial vestibular nucleus and nucleus prepositus hypoglossi abolishes all gaze-holding function in the horizontal plane.[68] In the vertical plane, the interstitial nucleus of Cajal also contributes to gaze-holding.[69] The way that the vestibular nucleus achieves gaze-holding (neural integrator) properties has also been addressed using a neural network approach, which has provided some interesting insights such as the effects of lesions upon this network[70,71] and the manner that recovery from a peripheral vestibular lesion may occur.[72]

Brainstem syndromes due to lesions of central vestibular pathways. The conceptualization of the vestibular system as a neural network carries certain clinical implications. Thus, lesions affecting central vestibular pathways often involve not only eye movements, but also postural stability and vestibular sensation. For example, patients with downbeat nystagmus show disorders of other eye movements, such as defective smooth pursuit and gaze-holding capability; they also show a significant fore-aft postural instability that can be interpreted as a direction-specific vestibulo-spinal imbalance since it is observed when the eyes are closed.[73] Despite the diverse, distributed nature of the sensitivity vectors shown by vestibular nucleus neurons, most patients with central vestibular disorders predominantly show their abnormalities in three major planes[1]: (1) disorders of the VOR in horizontal (yaw) plane—horizontal nystagmus and rotational vertigo; (2) disorders of the VOR in the sagittal (pitch) plane—downbeat or upbeat nystagmus; (3) disorders of the VOR in frontal (roll) plane—ocular tilt reaction, lateropulsion, skew deviation, cyclorotation of the eyes, and torsional nystagmus. This attribution of some characteristic ocular motor disorders to plane-specific vestibular pathway lesions is a first hypothetical and speculative attempt to classify vestibular brainstem disorders. It is based on clinical experience and animal studies showing that the several syndromes such as downbeat nystagmus, upbeat nystagmus, or ocular tilt reaction can result from distinct and separate lesions of vestibular pathways at different brainstem levels from the medulla to the mesencephalon. Pathways that mediate the VOR in either one of the three major planes indeed travel separate from each other within the ipsilateral or contralateral medial longitudinal fasciculus, the

brachium conjunctivum, or the ventral tegmental tract.[1,2] Such a classification is helpful for the clinician in terms of pathophysiologic thinking and topologic diagnostics. A rigid three-plane scheme is, however, too simple to cover current knowledge of the complex vestibular neuronal network. For example, patients with central vestibular disturbances may have disorders of eye movements that correspond to the planes of the semicircular canals.[74] Furthermore, accurate measurement of eye movements in all three planes in patients with downbeat nystagmus often reveals associated torsional components (personal observation). Finally, experimental lesions of the vestibular nucleus—either electrolytic[75] or pharmacologic[76]—produce various combinations of horizontal and vertical nystagmus, compatible with the concept of the vestibular nuclei as a distributed, parallel system. An important area for future research will be modeling of the vestibular network incorporating subpopulations of neurons according to their pharmacologic definition.

In conclusion, better understanding of the VOR has arisen from two main sources: (1) an appreciation that the VOR principally evolved to cope with the head perturbations that occur during natural activities, especially locomotion; and (2) the discovery that the vestibular system utilizes not just vestibular but also visual and somatosensory afferents, and contributes to stability of gaze and posture and the perception of body motion using a distributed parallel network of neurons. These conceptual advances have led to new, more natural methods of studying the VOR—as an integral part of the sensorimotor vestibular response—and more accurate mathematical representations of how the vestibular system achieves its goals.

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