Chapter 2

The Vestibular-Optokinetic System

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SUMMARY

This chapter deals with the ocular motor subsystems that hold images steady upon the retina during motion of the head. This ocular gyroscopic function guarantees clear and stable vision during natural activities that induce head perturbations, such as locomotion (Fig. 7–1). To hold gaze steady, the brain primarily uses labyrinthine and visual cues, though in disease, information from muscle spindles and joint receptors may also substitute for deficient vestibular signals.

Historically, quantitative descriptions of vestibular and optokinetic behavior long preceded any knowledge of the substrate for these reflexes. The labyrinth itself received its name from Galen in the second century AD when he first peered into the inner ear and noted the similarity to the Cretin 'labyrinthos'.[388] In 1796, Erasmus Darwin described how body rotation induced movement of the eyes [183] and, in 1819, Purkinje reported how optokinetic nystagmus and sensations of movement were produced while watching a cavalry parade.[359] The mechanisms for these phenomena were unknown and the prevailing notion was that sensations of movement emanated from cutaneous receptors that detected displacement of the body fluids. The important role of the vestibular organ in initiating eye movements that compensate for head movements was first demonstrated by Flourens [289] and later elaborated upon by Ewald.[271] These pioneers noted that opening or applying pressure to the lumen of the semicircular canals of animals produced movements of the head or eyes in the plane of the canal being stimulated. Ewald also first emphasized that there must be resting tone in the vestibular nuclei even when the head was still. This discovery of the significance of the vestibular organ led to systematic clinical study of vestibular function. Bárány[68] formalized aspects of rotational testing and introduced positional and caloric stimulation of the vestibular labyrinth. Mach[394] and Ter Braak[795] predicted, based upon human and animal studies, that vestibular and visual information must interact centrally, a notion that was confirmed by modern neurophysiologic research. Steinhausen[772] developed the mathematical equations to describe how the cupula is able to transduce head motion. In more recent years, pioneers in vestibular physiology including among others, Geoffrey Melvill Jones and Victor Wilson,[551,552,879] Jay Goldberg and César Fernández,[12] and Bernard Cohen,[185,186,189] have made vestibular research a major focus of both basic and clinical neuroscience.

In this chapter, we will (1) identify the functional demands made of the vestibular-optokinetic system during natural activities; (2) discuss its inner workings; (3) summarize the quantitative performance of this system in response to natural and laboratory stimuli; (4) describe testing of patients with vestibular disease; and (5) apply these principles to understand the pathophysiology of vestibular disorders. A glossary of commonly used terms and abbreviations appears in Table 2–1. Throughout the chapter, we refer to Video Displays on the accompanying DVD, which illustrate tests of the vestibular system and important physical findings.

Table 2–1. **The Vestibulo-Optokinetic System: A Glossary of Terms and Abbreviations**

Circularvection	Illusion of self-rotation induced during optokinetic stimulation
Eccentric rotation	Rotation around an earth-vertical axis with the head located away from the usual head-centered axis of rotation
Gain	Ratio of output (e.g., eye velocity) to input (e.g., head velocity)
Ocular counterrolling	Torsional rotations of the eyes induced by rolling the head, ear to shoulder. During rotation the response is generated by the rotational vestibulo-ocular reflex (r-VOR). When the head is kept in the tilted position, the torsional response is driven by a static otolith-ocular reflex
OKN	Optokinetic nystagmus
OKAN	Optokinetic after-nystagmus (usually measured in darkness), which follows a period of optokinetic stimulation

(Continued on following page)

Table 2–1. *(continued)*

Oscillopsia	Illusory, to-and-fro movements of the environment
OVAR	Off-vertical axis rotation. Rotation about an axis tilted away from earth-vertical
Phase	Measure of the temporal synchrony between input (e.g., head velocity) and output (e.g., eye velocity)
Time constant	Time taken for slow-phase eye velocity to decline to 37% of its initial value after the onset of a velocity-step stimulus
Velocity step stimulus	Sudden acceleration ("impulse") to a constant velocity rotation
Velocity storage	Central vestibular mechanism whereby the peripheral labyrinthine response is prolonged or perseverated. Optokinetic after-nystagmus (OKAN) is also generated by this mechanism
Vertigo	Illusion of movement (usually turning) of self or environment
VOR	Vestibulo-ocular reflex
r-VOR	Rotational VOR, compensatory slow phase driven by the semicircular canals in response to angular motion of the head
t-VOR	Translational VOR, compensatory slow phase driven by the otolith organs in response to linear motion of the head

FUNCTION OF THE VESTIBULAR-OPTOKINETIC SYSTEM

Head Rotations and Translations

The vestibular system must respond to both the angular (rotational) and linear (translational) components of head motion. To be more precise, rotations of the eyes must compensate for movements of the orbits. Angular and linear motions of the head are sensed by different structures. The semicircular canals respond to angular acceleration and the otolith organs respond to linear acceleration. Together, they provide the inputs for the vestibulo-ocular reflex or VOR. The response to the *rotational* (angular) component of head motion is called the r-VOR, and the response to the *translational* (linear) component of head motion is called the t-VOR. A third type of VOR—ocular counterroll—also is mediated by the otolith organs and reflects a response to linear acceleration, but, in this case, the stimulus is a change in the static orientation of the head with respect to the pull of gravity. There is a small change in static torsion (counterrolling) of the eyes in the opposite direction to a sustained head tilt.

The r-VOR responds to the three possible directions of head rotation, producing horizontal (around the rostral-caudal, yaw, or z-axis), vertical (around the interaural, pitch, or y-axis), and torsional (around the naso-occipital, roll, or x-axis) eye movements. The t-VOR responds to the three possible directions of head translation, producing horizontal (heave or side to side, along the interaural axis), vertical (bob or up and down, along the dorso-ventral axis), and vergence (surge or fore and aft, along the naso-occipital axis) eye movements, though the exact pattern of eye movements also depends upon where they are in the orbit.[347] Since the eyes are horizontally separated and the axis of rotation of the head is usually behind the eyes, rotational head movements almost invariably produce translations, or linear displacements, of the orbits. Even if the axis of rotation is centered on one orbit, the other eye will still be translated during rotation of the head with the only exception being pitch rotation around an axis passing though the center of both orbits. The ocular compensation required for translation of the orbits—during both rotations and translations of the head—is, of necessity, a function of the location of the point of regard. For rotations in yaw and pitch, the closer the object of interest, the larger must be the compensatory response to prevent unwanted motion of images on the retina. Furthermore, depending upon the location of the axis of rotation of the head relative to each of the two eyes (e.g., closer to one eye than the other), and the location of the object of interest relative to each of the two eyes (e.g., on the midline or off to one side), the brain must adjust the movements of each eye independently, so that they can both remain pointed at the object of regard during any pattern of head motion. For a more detailed analysis of the relationships among these variables, see Laboratory Evaluation of Eye-Head Movements, in Chapter 7.

Most naturally occurring rotational head perturbations are of high frequency (0.5 to 5.0 cycles/second), commonly due to vibrations from heel strike, which are transmitted through the body to the head during walking (see Figure 7–1). These head movements are compensated for, at least in part, by an oligosynaptic pathway consisting of three or four neurons. This pathway, the elementary VOR,[783] extends from the labyrinth to the extraocular muscles. The r-VOR has a latency of action (i.e., time from start of head turn to initiation of compensatory eye rotation) in the range of 7 ms to 15 ms largely depending upon the nature of the stimulus but also on the sensitivity of the recording system.[196] There is also a slight difference between the two eyes, possibly due to the additional abducens internuclear neuron in the horizontal VOR pathway to the medial rectus.[196] No other sensory mechanism that contributes to the generation of eye movements that compensate for head movements is so prompt in its action. If the VOR fails owing to disease, then vision during walking is impaired. The effects of "living without a balancing mechanism" were reported vividly by a physician who had lost labyrinthine function after receiving streptomycin.[437] When walking in the street, he could not recognize faces or read signs unless he stood still (see Video Display: Disorders of the Vestibular System). These symptoms indicate that visual-following reflexes, because of slow retinal processing, cannot adequately substitute for the VOR during natural head movements. Indeed, the latency of visual-mediated eye movements in humans is at least 75 ms.[323]

Head rotations in roll (around the naso-occipital axis of the head) place different demands upon the VOR than do head rotations in yaw (horizontally) or in pitch (vertically). This difference is because head movements in roll displace images away from the fovea much less than do head rotations in yaw or pitch; only in the periphery of the retina will appreciable slip of images occur. The torsional compensatory responses to head rotations in the roll plane need not be increased for near viewing since translation of the orbits during roll does not alter the needs for image stabilization for rotations of the globe around its line of sight. In this case, however, horizontal and vertical eye movements must be larger because of the increased requirements for compensation from the horizontal and vertical translation of the orbits. During roll head rotation the eyes can become misaligned vertically (producing a skew deviation) due to *translation of the orbits,* one up and the other down. Another cause for vertical misalignment during head roll is that the eyes rotate around an axis *parallel to the axis of head rotation* even when they are converged; thus one fovea moves up and the other down. Depending upon exactly where the eyes are in the orbit and how much the vertical t-VOR can compensate for the relative up and down motion of the two orbits, there can be varying degrees of vertical ocular misalignment. In essence, there are two competing needs during and after rotation of the head around the roll axis. First, there is a response to the need for full-field stabilization of the image on the retina during rotation, which when the head is rotating within a plane perpendicular to the ground (i.e., upright), also keeps the retinal meridians aligned with earth horizontal. Secondly, vertical misalignment and foveal disparity must be minimized to maintain single vision and stereopsis. Indeed some investigators have found suppression of the static and of the dynamic torsional VOR during near viewing, which would help prevent vertical diplopia[84,443,588] though other mechanisms such as torsional quick phases also help maintain eye alignment.[572]

Head Tilt

The otolith organs respond to linear accelerations. During translation of the head, its signals are transformed into the t-VOR. But the otoliths also respond to the pull of gravity, the most pervasive form of linear acceleration. Hence, when the attitude of the otoliths is altered relative to gravity, a tilt of the head is signaled and a compensatory reorientation of the eyes occurs. The action of this static otolith-ocular reflex can be seen clearly in afoveate, lateral-eyed animals such as the rabbit.[186] When the head is tilted laterally and kept there, the eyes are moved and held in a com-

pensatory position relative to earth horizontal (one up in the orbit and the other down, in a physiological skew deviation). When the head is pitched forwards or backwards, the eyes counterroll and are then held in their new position to keep the retinas aligned with the horizontal meridian. In human beings, if the head is pitched forward (chin to chest), the object of interest can be fixed upon using saccades, so that static compensatory eye movements to keep the retina aligned along the horizontal meridian are unnecessary. When the head is tilted laterally, a dynamic component, primarily mediated by the semicircular canals, preserves vision during the head movement. During sustained lateral head tilts, however, we still rely on the static otolith-ocular reflex that produces ocular counterrolling, because our ability to make voluntary torsional movements is limited. Counterrolling of the eyes in humans is vestigial and compensates for only about 10% of the head tilt.[39,103,197,628,641,645]

The relatively feeble ocular counterrolling to static head tilt does not seem disadvantageous for vision because changes in the torsional orientation of the retina have little effect on foveal acuity. Indeed for viewing near objects it may even be advantageous to have a lower gain of counterrolling to minimize any potential vertical misalignment (see Head Rotations and Translations). Nevertheless, a fundamental question in vestibular physiology is how, and to what degree, the vestibular system resolves the inherent ambiguity between translation and tilt.[13,14,557] The otolith organs respond in the same way to linear accelerations of any type, and their afferent discharge in itself does not allow for a distinction between tilt and translation. Recent experimental evidence suggests that information from the semicircular canals allows the brain to 'decide', through an internal model of the relationship of the head to the pull of gravity, if the change in otolith activity is due to a tilt or to a translation of the head.[14,34,35,73,564,565,910,912] Single-unit recordings in monkeys have revealed neurons within the brainstem and cerebellum that could represent internal models of the "physical equations of motion", and thus help resolve the inherent ambiguity in tilt versus translation, which is discussed below.[34,743,744] At the level of perception there appears to be a representation of the pull of gravity in the areas of cerebral cortex that receive vestibular inputs within which the motion of visual objects can be deciphered.[425] Furthermore, in response to otolith stimulation, subjective sensations and compensatory ocular motor responses may be dissociated, each meeting the specific functional needs for perception of self-motion and orientation and for stabilization of gaze and effective binocular vision.[559,560]

Vestibular-Visual Symbiosis

Both the t-VOR and r-VOR perform optimally in response to brief, high-frequency motion of the head. The ability of the r-VOR to transduce reliably the motion of the head fades during sustained, low-frequency head rotation. Consequently, other mechanisms must substitute for the declining vestibular response, and visual-following reflexes assume the burden of maintaining stability of images on the retina during prolonged (low-frequency) rotation of the head.[185,577,730] Specifically, the optokinetic system appears to have evolved to supplement the r-VOR. Its action is easily appreciated in lateral-eyed animals (such as the rabbit) that do not have foveae, and in which other forms of visual tracking such as smooth pursuit and vergence are rudimentary. Consider the rabbit as it moves in a large circle for 30 or 40 seconds, a typical response while the animal is being chased by predators. The rotational component of this movement will have a low frequency. Because of the mechanical properties of the semicircular canals, the r-VOR, by itself, can only hold the eyes steady during the first few seconds of turning (the cupula slowly returns toward its initial position during a sustained rotation). As the animal moves around the circle, vestibulo-ocular compensation declines and visual images of the world increasingly slip across the retina. This is the stimulus to the optokinetic system. Consequently, vestibular compensation is replaced by optokinetic visual following during sustained self-rotation.

When the optokinetic system is tested artificially in the rabbit, in isolation (for example, using a drum rotating around the animal to produce a sudden movement of the visual surround at a constant velocity), the optokinetic response slowly builds (charges) over time until it reaches a velocity close to that of the stimulus.[194] Then, if the lights are turned off, the optokinetic system slowly discharges, producing an optokinetic after-nystagmus (OKAN). This charging and discharging behavior is just the backup that is needed to substitute for the fading vestibular response during rotation in the light and to help suppress the unwanted post-rotatory vestibular nystagmus that occurs when the rabbit suddenly stops its sustained rotation. These optokinetic responses are mediated centrally by the Velocity-Storage Mechanism (see below).

The t-VOR has similar limitations in its ability to transduce low-frequency stimuli, in this case in response to linear motion of the head. Pure translations of low frequency are partially misinterpreted as tilts of the head with respect to gravity. They elicit both ocular counterroll and compensatory slow phases of vertical or horizontal nystagmus.[14,559,560,794] These low-frequency isolated translational stimuli, however, are unlikely to occur naturally. The actions of the t-VOR are best seen in foveate animals under more natural conditions, in which case translations are usually of higher frequency and commonly combined with rotations of the head. In lateral-eyed animals, the t-VOR and visual-following responses are rudimentary; a robust translational response in a lateral-eyed animal could actually become a hindrance during forward motion in the environment by pinning the eyes onto the visual scene behind the animal. The inherently poor optokinetic response of lateral-eyed animals to nasal-temporal directed motion could reflect the need to avoid inappropriate visual stabilization during forward locomotion.[858]

Once animals became frontal-eyed and developed foveae, they evolved systems to focus their lines of sight in a particular depth plane, necessitating compensatory responses for head translation that depended upon viewing distance.[577] Likewise, the visual-driven compensatory response for translation of the head depends upon the distance of the target of interest. To maintain fixation of objects of interest moving in a particular depth plane, two mechanisms are required. First, there must be a disjunctive mechanism—vergence—for maintaining the alignment of eyes for the desired depth plane, and second, a conjugate mechanism—pursuit—for keeping the line of sight on the particular target of interest within the desired depth plane. As might be predicted, the frequency ranges in which the t-VOR and pursuit function optimally are complementary.[794] The t-VOR and pursuit also behave similarly with respect to associated torsion. They obey Listing's law (discussed in Chapter 9) rather well in contrast to the r-VOR, which does not.[2,850]

With the evolution of binocular, foveate vision, circumstances arise when there might be a conflict between the needs for stabilization of images on the fovea and for stabilization of images on the rest of the retina. This might occur, for example, when fixing upon a small object relatively close to oneself, while walking. The more distant background would move on the retina in the opposite direction. In these circumstances, the pursuit system, with its attentional focus, dominates visual following. A similar response can be seen when foveate animals are subject to artificial movement of the visual environment, such as within an optokinetic drum or with a visual scene projected onto a tangent screen. There is an immediate, almost involuntary pre-attentive response, variously called the direct, early, rapid, or immediate component of optokinetic nystagmus (OKN) or, more simply, the ocular-following response.[577] This response is likely mediated by pursuit pathways, though with a shorter latency than seen with the onset of pursuit tracking of a small target.[2,790] Perhaps with a full-field stimulus, the time for the attentional decision-making processes that are associated with voluntary pursuit of small objects can be bypassed. In humans, optokinetic nystagmus is dominated by smooth pursuit, blurring the distinction.

Vestibulo-ocular reflex suppression or cancellation of the VOR refers to modulation of VOR responses during combined eye-head tracking, when the object of interest is not stationary but moves in the direction of the head. The mechanism is related to smooth pursuit and is discussed in Chapter 7.

ANATOMY AND PHYSIOLOGY OF THE PERIPHERAL VESTIBULAR SYSTEM

The Structure of the Labyrinth

The membranous labyrinth lies within its bony counterpart in the temporal bone, cushioned by perilymph (Fig. 2–1, top left).[523,879] It contains the cristae of the semicircular canals,

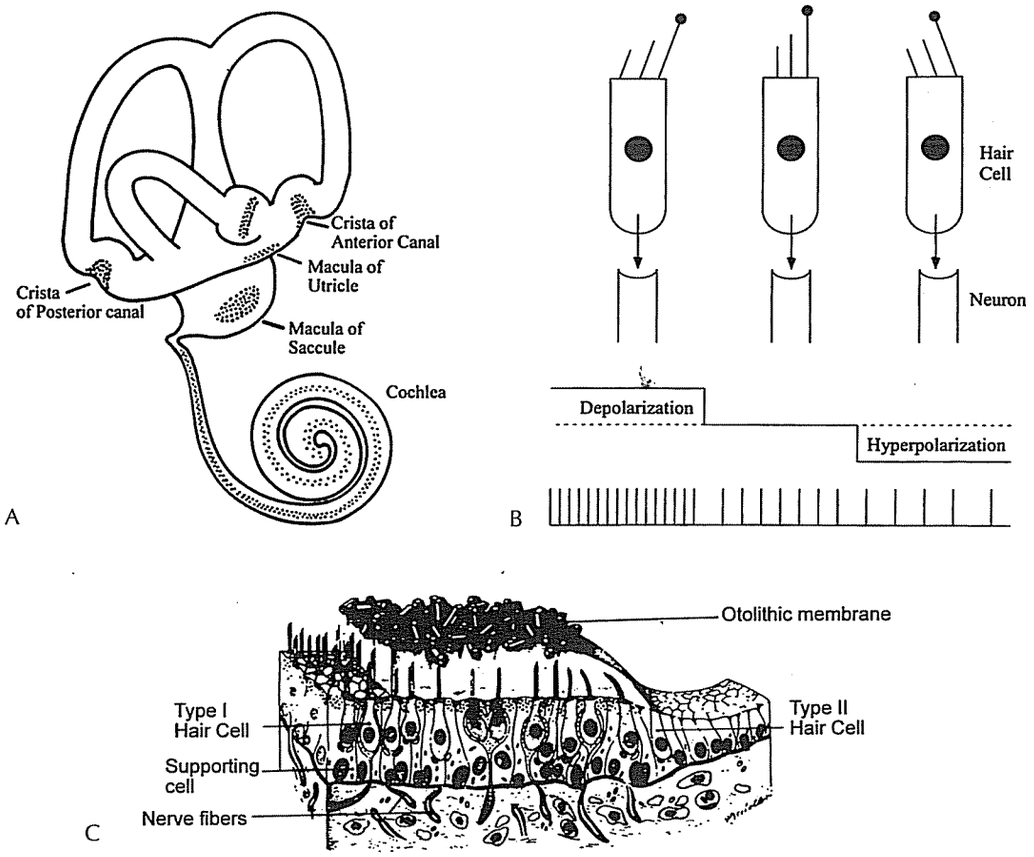

Figure 2–1. (A) Schematic of the mammalian labyrinth. The crista of the lateral semicircular canal is shown but not labeled. (B) Motion transduction by the vestibular hair cells. At rest there is a resting rate of action potential discharge in the primary vestibular afferents (center). Shearing forces on the hair cells cause depolarization (right) if the stereocilia are deflected toward the kinocilium (indicated by longest cilium, with beaded end), or hyperpolarization (left) if the stereocilia are deflected away from the kinocilium. This modulates the discharge rate in the vestibular nerve (neuron). (C) Schematic drawing of a macula, showing how the cilia of the hair cells are embedded in the gelatinous otolith membrane, to which are attached calcium carbonate crystals—otoconia. (A redrawn from Wersall DJ, Bagger-Sjoback D. Morphology of the vestibular sense organs. In Kornhuber HH (ed): Handbook of Sensory Physiology, Vol. VI/1, Vestibular System. Springer, New York, 1974, pp 123–170, with permission. B from Precht W,[669] with permission. C adapted from Iurato S. Submicroscopic Structure of the Inner Ear, Pergamon Press, Oxford, 1967.)

which sense head rotation, and the maculae of the utricle and saccule, which sense linear motion and static tilt of the head. Both cristae and maculae contain specialized hair cells of two forms (Type I and Type II, defined by the presence or absence of a calyx or chalice) that transduce mechanical shearing forces into neural impulses. The processes of each hair cell consist of many stereocilia and one kinocilium. The cilia are aligned so that they react best to shearing forces applied in a specific orientation. Deflection of the stereocilia toward the kinocilium causes depolarization (stimulation) of the hair cell; deflection in the opposite direction causes hyperpolarization (inhibition) (Fig. 2–1, top right).[530] The processes of the hair cells of the cristae are embedded in a gelatinous, sail-like structure, called the cupula. One cupula lies in each of the ampullae (regions of enlargement) of the three semicircular canals. Each turning movement of the head causes the endolymph within the semicircular canals to lag behind and to bend the cupula and so change the discharge of the hair cells that lie at its base.

The hair cells of the maculae also have their processes embedded in a gelatinous membrane, but attached to this are calcium carbonate crystals called otoconia (Fig. 2–1, bottom). The main stimulus to the macula is linear acceleration of the head, including the gravitational pull on the otoconia. The arrangement of the hair cells on the macula, which is more complex than that of the cristae, enables detection of any linear motion permitted by 3-D space. Hair cells of opposite polarization tend to be aligned on either side of a central stripe of hair cells called the striola. The macula of the utricle lies approximately in the horizontal plane and the macula of the saccule approximately in the parasagittal plane. They respond best to linear accelerations in these planes, though both are curved structures like ellipsoids and respond, to some degree, to linear acceleration in any direction.[438,439,601,602] It has been suggested that the lateral portion of the utricle may respond best to translations and the medial portion to the pull of gravity.[503] This idea, coupled with the phenomenon of 'cross-striolar inhibition' in which activation of hair cells on one side of the striola can inhibit activity in hair cells on the other (discussed below), would account for the seeming paradox that patients with a unilateral loss of labyrinthine function have a deficit in the t-VOR when translated toward the side of the lesion, and a deficit in ocular torsion when tilted toward the side of the lesion.[354] Neurophysiologic evidence for this hypothesis is awaited.

The Blood Supply and Innervation of the Labyrinth

The **blood supply** of the membranous labyrinth is from the internal auditory or labyrinthine artery.[537,876] The labyrinthine artery usually arises from the anterior inferior cerebellar artery (AICA), but sometimes arises directly from the basilar artery. After giving a branch to the eighth nerve in the cerebellopontine angle, the internal auditory artery traverses the internal auditory meatus. When it reaches the labyrinth, it branches into (1) the anterior vestibular artery, which supplies the anterior and lateral semicircular canals and most of the utricular macula and a small portion of the sacculus; (2) the vestibulo-cochlear artery, with two rami—cochlear and vestibular (the latter is also called the posterior vestibular artery, and supplies primarily the posterior semicircular canal and the saccular macula); and (3) the main (proper) cochlear artery. The internal auditory artery is an end artery; when it or its source, the AICA, is occluded, inner ear function is lost (see Video Display: Cerebellar Syndromes). Selective occlusion of branches of the internal auditory artery, such as the anterior vestibular artery, may cause selective loss of labyrinthine function.[287,339,620]

Nerves from the cristae and maculae pass through the perforations of the lamina cribrosa to reach Scarpa's ganglion at the lateral aspect of the internal auditory canal. The vestibular nerve is divided into two branches: (1) the superior division, which innervates the anterior and lateral semicircular canals and the utricle, and (2) the inferior division branch, which innervates the posterior semicircular canal and most of the saccule. This anatomical separation has important clinical implications with respect to a predilection for viral infections to involve the superior division (see Chapter 11). A small branch from the superior vestibular nerve (Voit's anastomosis) innervates the anterosuperior part of the saccule. The superior branch runs with the facial nerve, and the inferior branch runs with the cochlear nerve. A small number of vestibular fibers may also run in the cochlear division. The anterior vestibular artery supplies the structures innervated by the superior branches of the vestibular nerve, and the posterior vestibular artery supplies structures innervated by the inferior branches. From Scarpa's ganglion, the vestibular nerve passes medially, traversing the cerebellopontine angle. It then lies posterior to the cochlear nerve and below the facial nerve, entering the brain stem between the inferior cerebellar peduncle and the spinal trigeminal tract, to synapse in the vestibular nuclei.[607]

The Mechanical Properties of the Semicircular Canals and Otolith Organs

The physical properties of the labyrinthine motion sensors are important determinants of the overall vestibular responses. The crista ampullaris is most sensitive to brief head turns, because of the physical properties of the cupula and surrounding endolymph, which have been likened to those of an overdamped

torsion pendulum.[163,772,879] The internal diameter of the semicircular canals is small relative to their radius of curvature, so, given the hydrodynamic properties of the endolymph, the motion of endolymph—and hence the change in the position of the cupula—caused by a head rotation is approximately proportional to head velocity.[225,879] Thus, the semicircular canals mechanically integrate the angular head acceleration that they sense, allowing them to provide the brain with a head-velocity signal. This has been confirmed electrophysiologically by recording from semicircular canal afferents in the vestibular nerve.[276,332] Another consequence of these mechanical features is that only a small amount of endolymph displacement occurs, even with high-acceleration head turns, and the cupula is not in danger of being excessively displaced. With sustained head rotations, the elastic properties of the cupula become important and cause it to return to its resting position with an exponentially decaying time course. The time constant of return of the cupula cannot be directly measured in humans, but has been estimated to be about 6 seconds.[185,303,592]

The return of the cupula to its resting position can be related to the decline in nystagmus during velocity-step rotations (an impulse of acceleration to some constant velocity). This per-rotational nystagmus is greatest at the onset of the stimulus, but then slow-phase velocity shows an approximately exponential decline. If the subject is suddenly stopped after a sustained, constant-velocity rotation, post-rotational nystagmus will be produced. This reflects displacement of the cupula in the direction opposite to that when the rotation began. In animals, and probably humans, per-rotational nystagmus lasts considerably longer than the time required for the cupula to drift back to its starting position. This suggests that the brain manipulates the canal signal so as to prolong the time that motion of the head can be perceived. This phenomenon is mediated by the velocity-storage mechanism, and is common to both vestibular and optokinetic responses.

Flow of endolymph within each canal, in one direction, produces excitation in its ampullary nerve (increasing its discharge rate) and, in the other direction, produces inhibition. For the lateral (or horizontal) canals, flow toward the ampulla (ampullopetal flow) is excitatory. For the vertical canals, flow away from the ampulla (ampullofugal flow) is excitatory. The semicircular canals are arranged so that each canal on one side of the head is paired with another on the opposite side, both lying in nearly the same plane. Careful measurements have shown that the relative planes of the three canals vary among individuals,[224] however, and complementary canals on opposite sides of the skull may not be precisely aligned.[241,787] Clearly the brain must make adjustments for such individual variations. Despite these small differences, the semicircular canals can be thought of as working in pairs. Thus, an ampullofugal flow of endolymph within the right anterior semicircular canal will be accompanied by an ampullopetal flow in the left posterior semicircular canal. This push-pull arrangement stands the organism in good stead in the event that disease should destroy one labyrinth, since the brain can then still use a (normal) decrease in activity from the intact labyrinth to detect head rotation toward the side of the lesion. The effects of stimulating individual semicircular canals are summarized in Figure 2–2A. Each canal produces movements of the eyes in the plane of that canal (described by Flourens for head movements (Flourens' law) and Ewald for eye movements (Ewald's first law)).[211,212,629] These findings have important clinical significance, which is discussed later in this chapter in the section on disorders of the vestibular-optokinetic system.

The physical properties of the otolith maculae are more difficult to analyze than those of the semicircular canals, in part because they are curved structures, and so sense linear acceleration in many different directions.[220,439] The utricular macula lies on the floor of the utricle, approximately in the plane of the lateral semicircular canals. The saccular macula lies on the medial wall of the saccule, nearly parasagittal with respect to the head (i.e., in a plane approximately orthogonal to the utricular macula). The utricle is oriented to respond best to lateral or fore-and-aft tilts, and side-to-side translations of the head. The saccule is oriented to respond best to up-and-down translations of the head. Hence these two otolith organs serve complementary roles in sensing gravitational and other linear forces applied to the head. Because the maculae are located eccentric to the axes of rotation of the head, they are able to sense both tangential and centrifugal forces during head rotations.

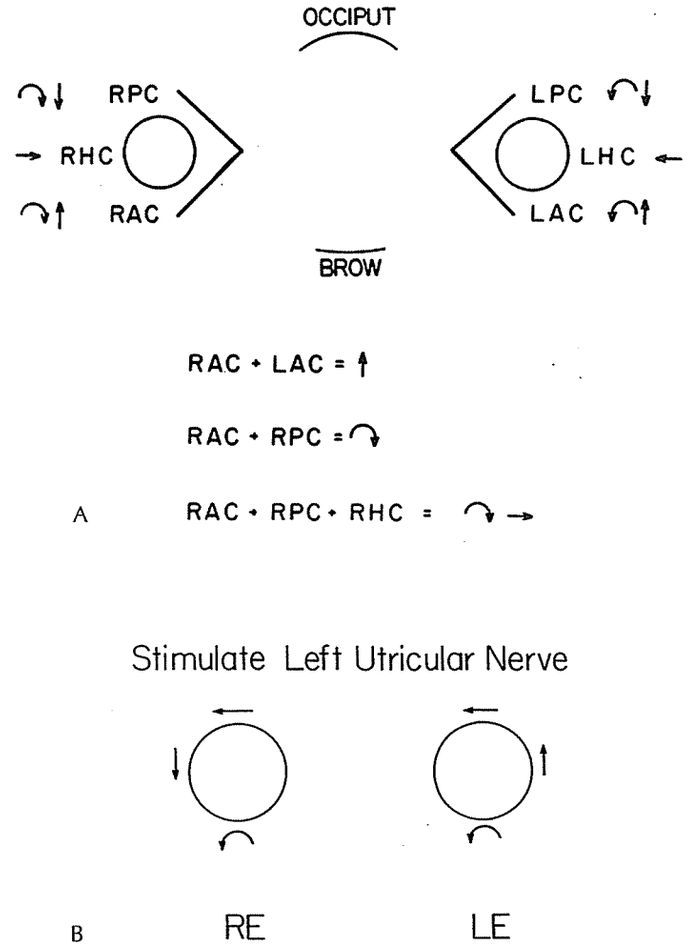

Figure 2–2. (A) Schematic summary of the ocular motor effects of stimulating individual semicircular canals and combinations of canals. Stimulation of a single canal produces slow-phase movements of the eyes in a plane parallel to one in which the canal lies. As shown by the equations at the bottom, purely vertical nystagmus can only be induced by simultaneous stimulation of the same canal on both sides. Purely torsional nystagmus can only be produced by stimulation of both vertical canals, but not the lateral canal, on one side. Thus, disease of the labyrinth seldom produces purely vertical or purely torsional nystagmus. Combined involvement of all three canals on one side causes a mixed horizontal-torsional nystagmus. (B) The effects of left utricular stimulation. Besides torsional eye movements, there is a vertical deviation of the optic axes (skew deviation) and horizontal deviation away from the side of stimulation.

The mechanism of action of the otoliths is an inertia-generated shearing movement of the otoconial layer, parallel to the underlying surface of the sensory epithelium. In this way, the otoliths can sense both translational head movements (i.e., linear accelerations) and static tilts of the head (with respect to the pull of gravity). Electrical stimulation of the utricle and saccule produces various patterns of eye movements including upward movement of the ipsilateral eye and downward movement of the contralateral eye with torsion.[219,337,338] Similar results are produced by stimulation of the utricular nerve, although there is also a horizontal component. (Fig. 2–2B)[780] The results of these stimulation studies must be interpreted cautiously because of issues such as current spread, effects of anesthesia, and the differences in responses depending upon which particular part of the macula is stimulated. Behavioral studies also suggest that the saccule can contribute to ocular torsion, and perhaps to disconjugate torsion.[237] It must be reiterated that the otolith maculae are curved structures, not flat, and that both the saccule and utricle can respond, to some extent, to linear accelerations in any direction.

Neural Activity in Vestibular Afferents

The discharge properties of the vestibular nerve are distinguished by continuous spontaneous activity or resting vestibular tone.[331,332,403] For the semicircular canal afferents this resting

discharge frequency is modulated up or down during rotation of the head. The modulation of vestibular activity by rotational stimuli has been extensively studied in many species. For the physiologic range of head movements, the signal from the semicircular canals is a representation of rotational head velocity, though head acceleration is the stimulus that leads to excitation of the hair-cell receptors. The integration from acceleration to velocity is largely a mechanical one, related to the physical properties of the endolymph and semicircular canals, but the information about head motion carried by the afferents is also affected by the dynamics of transfer of information at the connection between the hair cell and its afferent nerve fiber. Thus, a transduction of the acceleration of the actual movement of the head to a signal proportional to the rotational velocity of the head carried on individual vestibular afferents is an oversimplification.[403,679] Rather it is the central processing of the ensemble of different types of peripheral afferent information that leads to the correct eye movement response to the motion of the head. Furthermore, adaptation to sustained (low-frequency) head rotations, in particular, seems to reflect a number of processes beginning from the hair cell itself, to the vestibular afferents and eventually, to the central networks within the vestibular nuclei and possibly the cerebellum. Again, the final, calibrated and optimized eye movement response to head motion must reflect the entire cascade of physiological processing of information within the complex anatomical organization that underlies the VOR.

Vestibular stimuli that are outside the natural range of head motion, for example, at especially high velocities or accelerations, or at especially low or high frequencies, present particular challenges to the ability of the vestibular periphery to reliably transduce head motion. For example, at high head velocities, when the discharge of one set of canal afferents is fully inhibited, the VOR will depend upon the excitatory response from one labyrinth alone. This asymmetry in response at high velocities leads to one form of Ewald's second law that, in its generic form, states that excitation is a relatively better vestibular stimulus than is inhibition. Ewald's second law becomes particularly evident when there is a loss of the function of the labyrinth on one side. Another equally important form of Ewald's second law may apply to the acceleration and frequency characteristics of head rotation (see Clinical Findings with Dynamic Vestibular Imbalance, below).

The nonlinear effects of Ewald's second law have important implications even in normal behavior. The r-VOR has a gain—ratio of output (eye velocity) to input (head velocity) —of 1.0 in normals for rotational velocities up to 350° per second– 400° per second,[675,705] even though vestibular afferents are presumably driven into inhibitory cutoff at velocities well below 200° per second.[276,276] Therefore, for high speeds of head rotation there must be a mechanism to compensate for the loss of the contribution of the afferents (disinhibition) on the side opposite to rotation (when these afferents are driven into inhibitory cutoff). Several suggestions have been made as to how central mechanisms ensure such a wide range of linear responses. One hypothesis is that when activity no longer comes from the inhibited labyrinth, there is a central disinhibition that increases the sensitivity of the response to afferent activity emanating from the excited labyrinth.[897] Alternatively, the presence of quick phases may prevent vestibular neurons from being driven into inhibitory cutoff and so improve their linear range of response.[313,759] Just as for the slow phases, the timing and amplitude of quick phases are also affected during vestibular compensation.[170,217,326] Finally, the combined effects of irregularly and regularly discharging afferents (see below) may help to make the reflex linear and enable it to respond to a wide range of frequencies and accelerations.[331,419]

DIFFERENT CLASSES OF VESTIBULAR AFFERENTS

Vestibular nerve fibers have been classified as regular afferents or irregular afferents, depending upon the regularity of their discharge rate, and both project to neurons within the vestibular nuclei that discharge in relation to the VOR.[120,331,333,383,581] The exact functional differences between irregular and regular afferents are uncertain, though theories abound. Regular afferents have tonic response dynamics, resembling the displacement of the cupula or of the otolith membrane, and have a low sensitivity to head rotations or linear forces. The caliber of their axons is medium to small and they end as dimorphic units and

bouton units in intermediate and peripheral zones of the cupula or macula. Irregular afferents have phasic-tonic response dynamics, including sensitivity to the velocity of cupula and otolith membrane displacement, and hence show acceleration sensitivity in the case of afferents from the semicircular canals, and 'jerk', the derivative of acceleration, in the case of afferents from the otolith organs. Their axons are medium to large.

Irregular afferents in the central zone of the cristae have low rotational sensitivities and terminate as calyx endings onto Type I hair cells. Irregular afferents located away from the center have high rotational sensitivities and terminate as dimorphic endings onto both Type I and Type II hair cells. The irregular canal afferents have been posited to play a role in VOR adaptation including the compensatory response to unilateral labyrinthine loss and especially for high-frequency and high-velocity rotational stimuli toward the side opposite the lesion. On the other hand, regular afferents may be involved in the compensatory response to unilateral labyrinthine loss for lower velocity stimuli for rotations to either side. Irregular afferents have also been posited to play a role in modulation of the VOR during eccentric rotation and for near viewing, in cancellation of the VOR, in the generation of the low-frequency, velocity-storage component of the VOR; and perhaps in extending the linear range of the VOR at high speeds of head rotation.[32,181,251,339,383,418,493,542,544] The inputs to the VOR from irregular afferents from the semicircular canals can be modulated at the vestibular nuclei according to context that we will discuss below.[172,216,544] The irregular otolith afferents may play a role in the generation of off-vertical axis rotation (OVAR), possibly through the velocity-storage mechanism.[33]. Both irregular and regular otolith afferents appear to contribute to the high-frequency, high-amplitude t-VOR.[27] It has also been suggested that the vestibular system compares activity between irregular and regular otolith afferents to distinguish tilt and translation.[911]

The neurotransmitter used by vestibular afferents appears to be glutamate,[231,239,546] though GABA may also play a role at the hair cell synapse.[413] Recent work has detailed specific involvement of the metabotropic glutamate, N-methyl-D-aspartate and the kainate/AMPA excitatory amino acid receptors.[761] Other transmitters including nitric oxide synthetase (NOS), opiode peptides, and purines may also have a role in modulation of peripheral vestibular transmission.

Not all fibers within the vestibular nerve are afferent. Some vestibular efferents carry impulses to the labyrinth, but their function in mammals is unknown.[331] They do not suppress unwanted vestibular responses during passively evoked combined movements of head and eyes[158] and do not appear to modulate activity in active versus passive head movements.[215] Perhaps they play some role in VOR adaptation as axon collaterals of vestibular efferents project to the cerebellar flocculus.[676,755]

BRAINSTEM ELABORATION OF THE VESTIBULO-OCULAR REFLEX

Anatomic Organization of the Vestibulo-Ocular Reflex

How the brain stem fashions the precise compensatory eye movements from the raw vestibular signals has been extensively investigated since Adrian first recorded the activity of neurons within the vestibular nucleus.[3,70,159,523] Of prime importance has been the study of the three-neuron arc: vestibular ganglion, vestibular nuclei, and ocular motor nuclei. Although this elementary vestibulo-ocular reflex arc[783] is readily equated with the notion of a rapidly acting reflex, parallel polysynaptic projections are equally important for generation of an appropriate, compensatory eye movement.[519] The direct neuronal pathways include both excitatory and inhibitory contributions.

Each semicircular canal directly influences a pair of extraocular muscles that move the eyes approximately in the plane of that canal, regardless of the initial position of the eye in the orbit. Important to the clinician is that disease selectively affecting one semicircular canal may produce nystagmus that rotates the globe in a plane parallel to that in which the canal lies (see, for example, benign paroxysmal positional vertigo (BPPV) or the syndrome of superior canal dehiscence, in Chapter 11). In summarizing pathways that mediate the r-VOR (Table 2–2 and Fig. 2–3), we have drawn largely on studies of central vestibular connections in primates,[159,165,214,543] but also mention pathways reported in other species.[70,167,523,823-825]

Table 2–2. **Direct Vestibulo-Ocular Projections as Determined by Electrophysiologic and Anatomic Studies in Monkey, Cat, and Rabbit**

Receptor	Effect	Muscle	Relay Nucleus	Pathway	Motor Nucleus
LC	Excitation	c-LR	M/LVN	MLF	c-VI
		i-MR	M/LVN	ATD	i-III
	Inhibition	i-LR	MVN	MLF	i-VI
		c-MR	—	Poly	c-III
AC	Excitation	i-SR	M/LVN*	MLF*	c-III
		c-IO	M/LVN*	MLF*	c-III
	Inhibition	i-IR	SVN	MLF	i-III
		c-SO	SVN	MLF	i-IV
PC	Excitation	c-IR	M/LVN	MLF	c-III
		i-SO	M/LVN	MLF	c-IV
	Inhibition	c-SR	SVN	extra	i-III
		i-IO	SVN	extra	i-III
U	Excitation	i-SO	LVN	MLF	c-IV
		i-SR	LVN	MLF	c-III
		i-MR	LVN	ATD	i-III
		c-IO	LVN	MLF	c-III
		c-IR	LVN	MLF	c-III
		c-LR	LVN	MLF	c-VI
S	Excitation		y-group	BC	

Muscles: LR: lateral rectus muscle; MR: medial rectus muscle; SR: superior rectus muscle; IO: inferior oblique muscle; IR: inferior rectus muscle; SO: superior oblique muscle; Relay Nucleus: M/LVN: medial and adjacent lateral vestibular nucleus (*: other nuclei and pathways such at the ventral tegmental tract, are also probably involved; see Figure 2–3); MVN: medial vestibular nucleus; SVN: superior vestibular nucleus; LVN: lateral vestibular nucleus; Pathway: MLF: medial longitudinal fasciculus; ATD: ascending tract of Deiters; poly: polysynaptic pathway lying outside MLF; extra: extra-MLF pathway; Motor Nucleus: VI: abducens nucleus; III: oculomotor nucleus; IV: trochlear nucleus; c-: contralateral; i-: ipsilateral. References: [340,541,543,669-671,780]

The anatomy of the vestibular nuclei in humans has been well characterized,[778] and most features are similar to those of nonhuman primates and other mammalian species.[159,399a,607] In humans, the volume of the vestibular nuclei is about 67 mm^3 and it contains over 200,000 neurons. Vestibular nuclei neurons receive projections from the vestibular nerve that contains about 14,000 to 18,000 axons. As a generalization, larger neurons in the vestibular nuclei receive labyrinthine input from axons of a larger caliber with an irregular discharge rate (perhaps type B vestibular nucleus neurons, see below); smaller neurons receive input from smaller-caliber axons, with a regular discharge rate (perhaps type A).[715] There are four major vestibular nuclei: medial vestibular nucleus of Schwalbe (MVN), lateral vestibular nucleus of Deiters (LVN), inferior or descending vestibular nucleus (DVN), and superior vestibular nucleus of Bechterew (SVN). In addition, there are several smaller accessory subgroups, including the interstitial nucleus (IN), with its cells distributed among the vestibular rootlets as they enter the brainstem, and the y-group, near the superior cerebellar peduncle. The MVN has the greatest volume and is the longest vestibular nucleus. Its rostral portion is a major receiving area for afferents from the semicircular canals and its cells project to the III, IV, and VI cranial nuclei, which mediate the vestibulo-ocular reflexes. Its caudal portionis reciprocally connected to the cervical region of the spinal cord, presumably mediating vestibulo-collic reflexes. The caudal MVN is also reciprocally connected to the cerebellum.

The rostroventral portion of the LVN receives afferents from the cristae of the semicircular canals and the macula of the utricle. Like the rostral MVN, it participates in vestibulo-ocular reflexes, in part through the

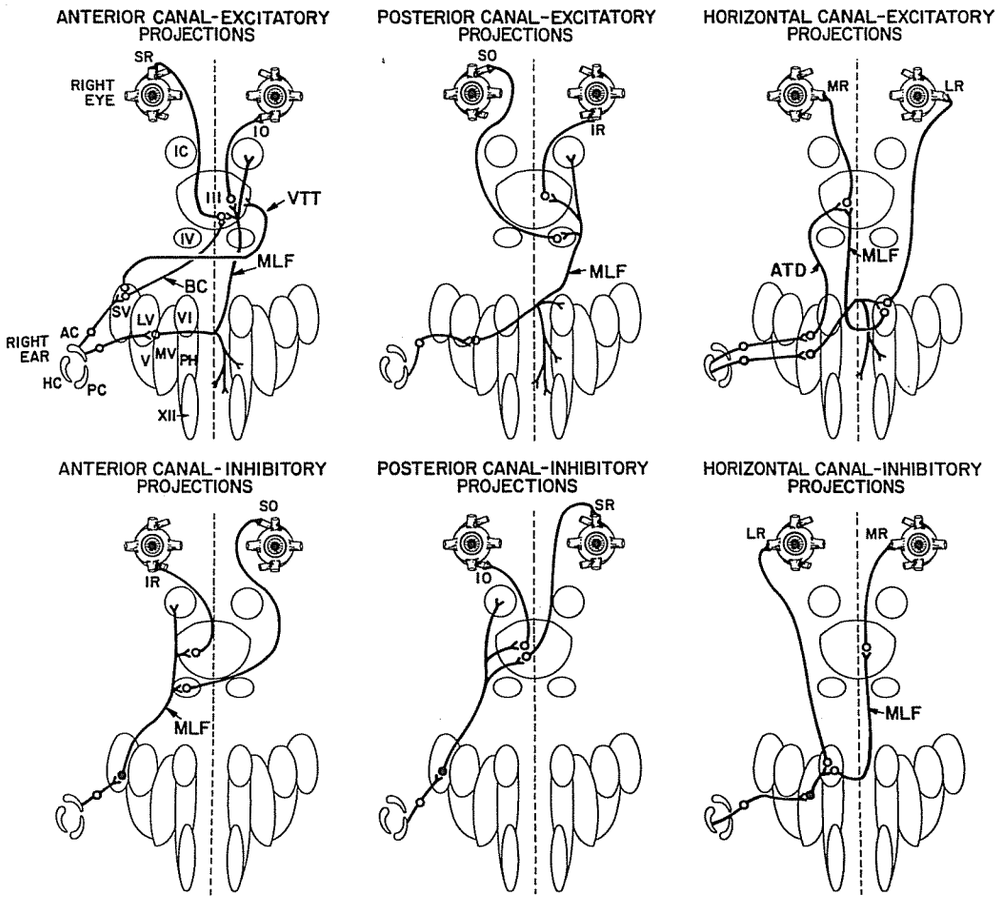

Figure 2–3. Summary of probable direct connections of vestibulo-ocular reflex, based upon findings from a number of species.[53,159,165,166,340,400,433,542,543,622,669–671,691] Excitatory neurons are indicated by open circles, inhibitory neurons by filled circles. III: oculomotor nuclear complex; IV: trochlear nucleus; VI: abducens nucleus; XII: hypoglossal nucleus; AC: anterior semicircular canal; ATD: ascending tract of Deiters; BC: brachium conjunctivum; HC: "horizontal" or lateral semicircular canal; IC: interstitial nucleus of Cajal; IO: inferior oblique muscle; IR: inferior rectus muscle; LR: lateral rectus muscle; LV: lateral vestibular nucleus; MLF: medial longitudinal fasciculus; MR: medial rectus muscle; MV: medial vestibular nucleus; PC: posterior semicircular canal; PH: prepositus nucleus; SV: superior vestibular nucleus; SO: superior oblique muscle; SR: superior rectus muscle; V: inferior vestibular nucleus; VTP: ventral tegmental pathway.

ascending tract of Deiters to the oculomotor nucleus. The LVN also has projections to the spinal cord, mainly via the ipsilateral lateral vestibulospinal tract but also through the contralateral medial vestibulospinal tract. In its most rostral aspect, the DVN also projects to the ocular motor nuclei.

There is considerable divergence of single primary afferents within the vestibular nuclei (about 15 neurons per axon). A single axon from a lateral semicircular canal can impinge upon neurons in the central part of the SVN, the rostral half of the MVN, the medial-rostral part of the DVN, and the ventromedial part of the LVN.

The primary vestibular afferents enter the medulla at the level of the lateral vestibular nucleus. Almost all afferents bifurcate, giving a descending branch to terminate in MVN and DVN and an ascending branch to the SVN, with a final destination in the cerebellum, especially the anterior vermis and the nodulus and uvula.[159,523,778] All canals and otoliths project to zone 1, which lies around the borders of ventromedial LVN, medial MVN, and dorsomedial DVN. All canals also converge on a small patch in the ventromedial SVN. These two areas contain the secondary vestibulo-ocular neurons that project to the abducens, oculomotor, and trochlear nuclei. Canal affer-

ents also converge on the interstitial nucleus of the vestibular nerve, which projects to the flocculus.

Utricular afferents project to the rostral MVN and saccular afferents project to the y-group. Some projections from the utricle overlap with those from the lateral semicircular canal, presumably reflecting their common roles in detecting horizontal motion; and some projections from the saccule, which is involved in detecting vertical motion, overlap with those from the vertical semicircular canals.[23,252,464,556,614,822,823,906,907] Recently, utricle and saccule projections were reinvestigated in the monkey.[614] Both project to the caudal descending vestibular nucleus presumably related to spinal mechanisms. The principal ocular motor areas within the brainstem to which saccular nerve terminated were the lateral portion of the superior vestibular nucleus and ventral nucleus y. The principal cerebellar projection was to the uvula with a less dense projection to the nodulus. Principle ocular motor brainstem areas of termination of the utricular nerve were the lateral/dorsal medial vestibular nucleus, and the ventral and lateral portions of the superior vestibular nucleus. In the cerebellum, a strong projection was observed to the nodulus and weak projections were present in the flocculus, ventral paraflocculus, bilateral fastigial nuclei, and uvula. Many of the central vestibular neurons that receive otolith afferents also project to the vestibulocerebellum.[626]

For both the horizontal and vertical r-VOR, many neurons in the vestibular nuclei that receive inputs from primary vestibular afferents encode not only head velocity, but also eye position, and varying amounts of smooth pursuit and saccadic signals.[13,15,16,213,216,541,544,555,706-708,731] A common and important cell type is the position-vestibular-pause (PVP) neuron. It encodes head velocity and eye position and becomes silent (pauses) during saccades. It appears to change its activity, depending upon whether vestibular stimulation is passive, as during steady fixation, or active, as part of a gaze change.[706,708]

Another cell type is the floccular target neuron (FTN), which receives inputs from both the labyrinth and the cerebellar flocculus and may be important in VOR adaptation.[96a,99,402,510] Additional cell types include those that show a sensitivity to eye and head velocity (EH, eye–head neurons), to head movement alone (VO, vestibular-only neurons), and to eye velocity and eye position burst-position (BP) neurons.[13,731] These secondary vestibular neurons may also show changes depending upon the particular combination of stimuli, including during cancellation of the r-VOR, during eccentric rotation, and comparing active versus passive head motion.[213,216,540,544,814] Vestibular nuclei neurons not only project to motoneurons; they also send axon collaterals to the nucleus prepositus hypoglossi (NPH) and the nucleus of Roller (see Table 5–1, and to the cell groups of the paramedian tracts (PMT) (see Box 6–4 in Chapter 6).[160,161] The NPH and adjacent medial vestibular nucleus (the NPH-MVN region, see Chapter 5) have a crucial role in holding gaze steady (neural integration). The cell groups of the PMT may be important for relaying an internal or efference copy of eye movement signals to the flocculus of the cerebellum.[161,609] In addition, certain cells in NPH that receive vestibular inputs project to burst neurons in the PPRF to trigger quick phases of nystagmus.[170,217,299,326,624] Finally, many secondary vestibular axons have dual projections, both rostrally as VOR neurons and caudally as vestibulo-collic neurons.[584]

Neurons within the vestibular nucleus also can be classified by their membrane properties as Type A (tonic firing rates, responding linearly) and Type B (phasic firing rates, responding nonlinearly) although there probably is a continuum.[701,740,835] Whether or not these different properties relate to the segregation of afferent activity into regular and irregular, or the so-called linear and nonlinear VOR pathways (see below) remains to be shown. Following unilateral labyrinthectomy, however, there are different patterns of change on the ipsilateral and contralateral sides in the Type A and Type B cell types suggesting they play separate roles in the mechanisms of adaptation to a unilateral loss of function (probably related to restoration of tone and increase of responsiveness to contralateral inputs).[82,83,700]

The main vestibulo-ocular projection neurons lie in zone 1 and the center of SVN. Zone 1 predominantly carries excitatory PVP cells, and is also the origin of the ascending tract of Deiters, which runs laterally to the medial longitudinal fasciculus (MLF) to impinge upon the medial rectus subdivision of the oculomotor nucleus (Fig. 2–3). Zone 1 is under little direct cerebellar influence. Inhibitory PVP cells

also lie in rostral MVN. The center zone in SVN contains predominantly burst-position cells (neurons that discharge with eye velocity and eye position); most are related to vertical canal inputs. These neurons, along with those in the dorsal y-group, the marginal zone (between MVN and nucleus prepositus), and the rostral MVN, are under the influence of the flocculus. In general, the peripheral areas of the vestibular complex are the source of intrinsic interconnections and commissural connections. They also receive projections from the cerebellar nodulus and the accessory optic nuclei. Taken together, this pattern of connectivity suggests that they play a role in the velocity-storage mechanism. The interstitial nucleus of Cajal (INC) receives axon collaterals from all secondary vestibular afferents that supply the oculomotor nucleus, and sends reciprocal projections, predominantly ipsilateral, to the vestibular nuclei (see Box 6–6, in Chapter 6).

VERTICAL SEMICIRCULAR CANAL PROJECTIONS

For the vertical semicircular canals, several important principles may be summarized. First, the excitation of the anterior semicircular canals produces upward and torsional eye movements (with the primary projections being to the ipsilateral superior rectus and contralateral inferior oblique muscles), and excitation of the posterior semicircular canals produces downward and torsional eye movements (with the primary projections being to the ipsilateral superior oblique and contralateral inferior rectus muscles).[211,212,629] Second, each vestibular nucleus neuron concerned with the vertical VOR contacts two motoneuron pools, one for each eye.[896] Third, excitatory projections from the vestibular nuclei cross the midline, but inhibitory connections do not. Fourth, the pathways taken by axons conveying the upward and downward VOR differ.[665]

For the *anterior canal system*, there may be three excitatory pathways by which information is carried rostrally for the vertical VOR. *Excitatory* PVP cells in the MVN or adjacent ventral lateral vestibular nucleus (VLVN) project medially and dorsally, crossing the midline caudally, differing with the projections of the posterior-canal PVP cells. After crossing, they ascend in or just below the MLF to contact the superior rectus and inferior oblique subdivisions of the oculomotor complex. Axon collaterals of these fibers project to the INC, the cell groups of the PMT, and the perihypoglossal nuclei, including NPH. Recall that the projections of the superior rectus subnucleus are crossed but those of the inferior oblique subnucleus are uncrossed. Thus, this excitatory pathway connects the anterior semicircular canal to the ipsilateral superior rectus and contralateral inferior oblique muscles (Fig. 2–3).

Another cell group, described in the cat, which may contribute excitatory inputs to the anterior canal system, lies in the SVN. Their axons cross the midline in the ventral tegmental tract, close to the medial lemniscus at the rostral pole of the nucleus reticularis tegmenti pontis (NRTP), and then abruptly turn rostrally, passing through the decussation of the superior cerebellar peduncle, to terminate mainly on the superior rectus and inferior oblique subdivisions of the oculomotor complex.[166] Also, in some species, the SVN projects rostrally, just near the brachium conjunctivum, to the oculomotor nuclei. Thus, three pathways may contribute to the generation of eye movements during stimulation of the anterior semicircular canal; the projections in primates have not yet been completely described.

Inhibitory neurons for the anterior canal system lie in the SVN. Their axons exit from the rostromedial aspect of this nucleus and course medially and rostrally in the lateral wing of the ipsilateral MLF, to contact superior oblique motoneurons in the trochlear nucleus, and inferior rectus neurons in the oculomotor nucleus. Axon collaterals project to NPH and to cell groups of the PMT. The neurotransmitter of these inhibitory vestibular neurons may be Gamma-aminobutyric acid (GABA).[230,239,546]

For the *posterior canal system*, PVP cells are also found at the junction of the MVN and VLVN. These *excitatory* neurons project rostrally, medially, and dorsally through MVN until, at the level of the caudal abducens nucleus, they turn medially and cross the midline beneath the NPH and abducens nucleus, ventral to the MLF. After crossing the midline, they enter the MLF and project rostrally to the trochlear nucleus and inferior rectus subdivision of the oculomotor complex. Axon collaterals also pass, via the MLF, to the NPH and PMT cell groups, and to the INC. The projections of the trochlear motoneurons are contralateral, but those of the inferior rectus are

ipsilateral. Thus, this excitatory pathway connects the posterior semicircular canal to the ipsilateral superior oblique and contralateral inferior rectus (Fig. 2–3). In addition, the posterior semicircular canal also projects to the contralateral abducens nucleus. This projection for horizontal eye movements perhaps reflects the somewhat tilted orientation of the posterior canals in the labyrinth so they are stimulated during rotation around the yaw axis and might make a contribution to the horizontal VOR.

Inhibitory neurons subserving the posterior semicircular canals are found in the SVN and rostral MVN. Their axons project through the pontine reticular formation to reach the ipsilateral MLF and then contact the superior rectus and inferior oblique subdivisions of the oculomotor complex. These neurons also contact PMT cell groups and the INC. Like the inhibitory neurons of the anterior canal system, these cells also may use GABA as an inhibitory neurotransmitter.[239,414,546]

HORIZONTAL SEMICIRCULAR CANAL PROJECTIONS

For the *lateral (or horizontal) canals*, PVP neurons are located in the ventral part of the MVN and adjacent VLVN. Most of these *excitatory* neurons course rostrally and medially through MVN, pass through or beneath the ipsilateral abducens or rostral NPH, and cross the midline at the level of the abducens nucleus or slightly rostral to it. Soon after crossing the midline, these axons give collaterals that either terminate in the abducens nucleus or project to the NPH and PMT cell groups. Some PVP neurons project rostromedially, passing through the abducens nucleus, and run in the ascending tract of Deiters (ATD) to terminate in the medial rectus subdivision of the ipsilateral oculomotor complex; some of these axons send collaterals to PMT cell groups. Thus, these excitatory pathways connect the lateral semicircular canal to the ipsilateral medial rectus and contralateral lateral rectus muscles (Fig. 2–3). The functional significance of the pathway through the ATD is uncertain, but it may relate to VORs associated with translation or near viewing.

Inhibitory pathways for the lateral canals pass from the MVN to the adjacent abducens nucleus; these neurons may use glycine as a neurotransmitter.[546] The medial rectus neurons are peculiar in having no known disynaptic inhibitory input, although a multisynaptic, extra-MLF pathway may play a role.[53,400]

OTOLITH PROJECTIONS

Central otolith projections for the t-VOR have been less well studied than those concerned with the r-VOR; current concepts are summarized in Figure 2–4. As discussed previously, in the monkey,[51,614] the principal projections from the saccule are to the ventral portion of the y-group, lateral SVN, and to the uvula and nodulus. The principal projections from the utricle are to the laterodorsal MVN, and ventrolateral SVN. There are also projections to the nodulus, flocculus, ventral paraflocculus, fastigial nuclei, and uvula. Based upon anatomy, saccule projections seem more important for vestibulospinal mechanisms. Experimental stimulation of the utricular nerve causes eye movements that suggest contraction of the ipsilateral superior oblique, superior rectus, and medial rectus, and the contralateral inferior oblique, inferior rectus, and lateral rectus muscles,[780] though under different conditions of anesthesia and different parameters of electrical stimulation primarily ipsilateral-directed horizontal eye movements can be elicited.[219,337] Experimental stimulation of the saccular nerve causes vertical eye movements with a preponderance for downward-directed slow phases.[219,338]

The interpretation of these results of experimental stimulation of the otoliths is confounded by the fact that all the hair cells are not oriented in the same direction on the macula (and hence with stimulation are not all excited in one direction and inhibited in the other) as is the case for the cupula and the semicircular canals.[439] Thus, artificial stimulation might elicit different directions of eye motion depending upon the location of the electrical stimulus. The level of anesthesia may also play a role in the nature of the response. Presumably central vestibular mechanisms are able to extract the needed information about head motion elicited in natural circumstances using 1) commissural pathways and so-called cross-striolar inhibition in which afferent inputs from one side of the macula influence activity from afferents on the other[621,823,826] and 2) concurrent signals from the vertical semicircular canals, which help to

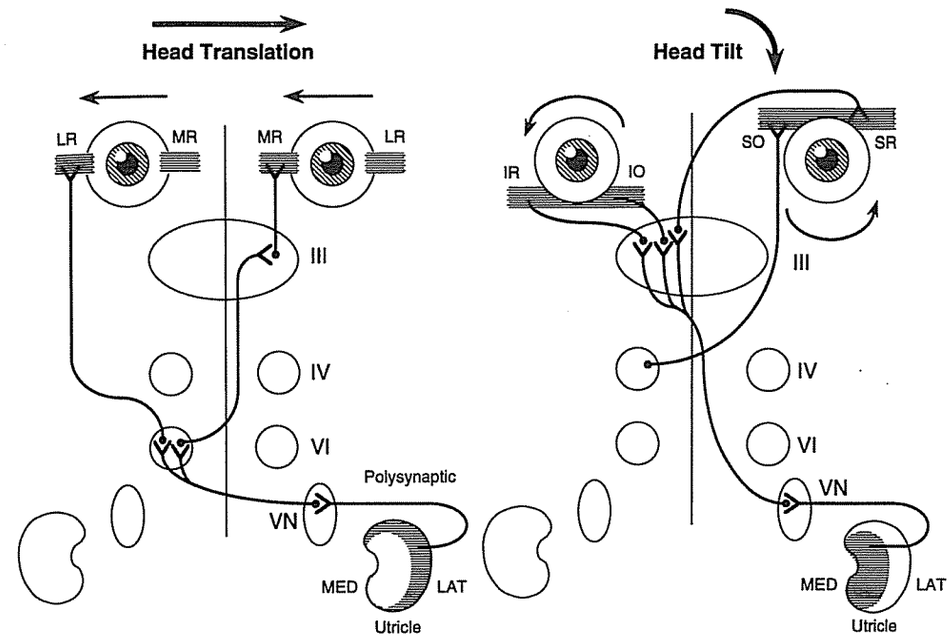

Figure 2–4. Hypothetical otolith pathways for tilt and translation. The medial portion of the utricle would be excited by ipsilateral head tilt and would lead to counterolling of the eyes by connections to the vertical torsional muscles. The lateral portion of the utricle would be excited by ipsilateral head translation and would lead to an oppositely directed horizontal slow phase presumably via polysynaptic connections, possibly through the cerebellum, to the horizontal muscles.

distinguish tilt from translation (see The Velocity-Storage Mechanism). Indeed, for generating the horizontal t-VOR, polysynaptic connections might arise from the lateral portion of the utricle, and reach the vestibular nuclei on the opposite side of the brain stem, possibly via the cerebellum, and are probably more important for the horizontal compensatory eye movements of the t-VOR than the direct projections to the ipsilateral vestibular nuclei.[13] On the other hand, projections from the medial portion of the utricle may be more important for signaling head tilt and lead to compensatory counterrolling using vertical torsional eye muscles.[354,503] Figure 2–4 shows such a scheme. Table 2–2 summarizes some of the direct anatomic pathways involved.

The vestibular nuclei also receive projections from a number of areas apart from the vestibular periphery. They include, of course, other brain stem nuclei, the cerebellum, and the cerebral hemispheres. As discussed below, vestibular neurons carry sensory information from the visual system as well as from proprioceptors and other somatosensory receptors in the neck and body. There are also large inputs from many areas in the cerebral hemispheres, reflecting the central role that the vestibular nuclei have in generating compensatory motor responses—during passive perturbations as well as self-generated movement, using information about spatial orientation and motion from all available sources (see Vestibular Sensation below).

A number of neurotransmitters have been implicated in synaptic transmission within and between the vestibular nuclei.[761] Glutamate, glycine, NOS, and GABA (especially related to commissural inhibition) are important. Hormonal receptors such as arginine-vasopressin, cannaboid receptors, and opioid-related receptors such as nociceptin, likely modulate synaptic transmission centrally.

Basic Neurophysiology of the Vestibulo-Ocular Reflex

The functional organization of the vestibulo-ocular responses is more complicated than the elementary anatomic connections suggest. For horizontal rotations, neurons in the vestibular

nuclei that encode head velocity can be divided into two main types. Type-I neurons increase their discharge rate for ipsilateral rotations and decrease their discharge rate during contralateral rotations; type-II neurons show the converse. Thus, each vestibular nuclear complex monitors rotation in both directions. This facility is aided by a vestibular commissure,[165] whereby ipsilateral type-I vestibular neurons drive contralateral type-II neurons. The organization of this vestibular commissure is specific, so that neurons in the right vestibular nucleus that receive input from the right lateral semicircular canal project to neurons in the left vestibular nucleus that are driven by the left lateral semicircular canal. A similar reciprocal connection is found for vertical canals (e.g., the right anterior canal and the left posterior canal). The vestibular commissure probably contributes to the velocity-storage mechanism (see next section).[189,345,461,863] Its precise role in vestibular compensation is unclear.[153,284,461]

A role for the vestibular commissure is less clear for otolith-ocular reflexes, being more certain for utricular than for saccular responses.[823,826] As described above, it has been shown that the equivalent of a push-pull relationship for saccular (and probably utricular) reflexes can be created on just one side of the brainstem.[825,826] This can be achieved by combining on the same vestibular nucleus neuron, monosynaptic excitatory inputs from one population of hair cells on one side of the striola, and disynaptic inhibitory inputs from another population of hair cells on the other side of the striola. This is called cross-striolar inhibition.

As described previously, vestibular nucleus neurons encode a range of sensory and motor signals: vestibular, ocular motor, visual, and somatosensory. Head velocity, the primary vestibular signal, is still present, but eye position is also encoded neurally. The presence of eye position signals on vestibular nucleus neurons reflects the crucial role played by the NPH-MVN region in gaze holding (neural integration of velocity-coded to position-coded signals); this role is discussed further in Chapter 5.

One must ask why there are so many different cell types within the vestibular nuclei, and why they each may carry multiple signals in varying proportions. Part of the answer relates to the complexity of the processing within the vestibular nuclei: inputs from the otoliths and semicircular canals are combined with visual and other sensory inputs within the brainstem to create a 'best estimate', using all available information, as to the orientation of the body and its motion within the environment. One part of this task is to decipher the source of any imposed linear acceleration: Am I translating or am I tilted? And the correct response must then be elaborated based upon where the eyes are in the orbit and the depth and location of the point of regard relative to each orbit. Indeed, much of the complexity arises from requirements related to the t-VOR. In the past few years, some order has emerged, based upon combining the results from single unit recordings in the vestibular nuclei during different patterns of motion, with novel computational models of how the different signals must interact.[34,344,345,692,911]

A neural network approach also has been used to account for the diversity of signals encountered in the vestibular nuclei.[9] The essence of this idea is that the central nervous system adjusts the activity of an ensemble of neurons for optimal vestibular performance even though there can be considerable variability amongst individual neurons as to exactly what signals they carry and to which head rotations they respond optimally.[8] The attractive feature of such a model is that it is able to predict and account for the seemingly paradoxical finding of individual neurons that carry velocity signals for movement in one direction, and position signals for movement in another.

The Velocity-Storage Mechanism

Vestibular neurons respond to sustained rotational stimuli with an initial increment in discharge rate that declines exponentially with the same time constant as the r-VOR (15 seconds), not as the cupula or vestibular nerve (6 seconds). So, as early in the pathway as the vestibular nucleus, the performance of the r-VOR has been improved. This central phenomenon, by which the raw vestibular signal is prolonged or perseverated, is accomplished by the velocity-storage mechanism. It improves the ability of the r-VOR to transduce the low-frequency components of head rotation.[693] During sustained (low-frequency) rotations, the velocity-storage mechanisms also function to realign the axis of eye velocity with the

direction of gravito-inertial acceleration (which usually calls for slow phases in a plane close to earth-horizontal). This effect, while seen in humans for small angles of lateral head tilt, is much more pronounced in monkeys.[18,21,226,280,282,327,692,694] Another related, and perhaps more fundamental, role for the velocity-storage mechanism may be in distinguishing tilt from translation so that the vestibular system can generate an appropriate t-VOR. Angelaki and Green have proposed a model for processing of linear acceleration signals, which has as a key component a head-velocity to head-position integrator used in distinguishing tilt from translation. It has been suggested that this integrator is identical to the velocity-storage integrator that determines the time constant of the r-VOR, though this remains to be proven.[13,34,344,345]

As noted above the vestibular commissure seems to be important for velocity storage. If it is sectioned, velocity storage is abolished.[412,461] Presumably interruption of pathways connecting the central portions of both MVN—the putative site for the generation of velocity storage—is responsible. Optokinetic afternystagmus (OKAN), the decaying after response that is seen when a subject is placed in darkness following sustained optokinetic stimulation; the bias component of off-vertical axis rotation (OVAR), discussed in the next paragraph; and the modulation of the direction and time constant of the r-VOR with changes in head orientation, are also lost after section of the vestibular commissure.[863] Thus, without velocity storage, the r-VOR generates slow phases in a head-coordinate system, regardless of the direction of gravito-inertial acceleration. Presumably, the ability to distinguish tilt from translation would also be lost after interruption of the vestibular commissure. Although achieved by central vestibular connections, velocity storage depends upon the tonic discharge of the vestibular nerves;[187] section of one vestibular nerve shortens the time constant of the r-VOR. Because optokinetic signals also are processed in this same velocity-storage mechanism, bilateral vestibular nerve section abolishes OKAN.[188,904] Visual fixation of a full-field, earth-stationary surround for even a few seconds largely discharges or nullifies activity within the velocity-storage mechanism.[185,849] Ablation of the cerebellar nodulus and uvula (see Box 12–3 in Chapter 12) maximizes velocity storage, except perhaps when torsion is stimulated.[17,846] Stimulation of the nodulus and parts of the ventral uvula discharge velocity storage, sometimes asymmetrically.[769] The velocity-storage mechanism can also be influenced by cervical inputs.[456] The velocity-storage mechanism is suppressed by baclofen; presumably it mimicks the inhibitory, GABAergic actions of Purkinje cells from the nodulus on to the vestibular nuclei.[184,226a,410-412,846]

Off-vertical axis rotation is the compensatory response induced when a subject's body is rotated around its own axis when it is tilted away from the vertical. During a constant-velocity rotation, there is an initial response from stimulation of the semicircular canals due to the r-VOR. As the response from the semicircular canals dies away, it is replaced by an otolith-mediated response consisting of a steady-state velocity (bias component of OVAR) and a component that changes with the gravity vector (modulation component of OVAR). The bias component derives from the velocity-storage mechanism, and the modulation component from the direct otolith signal.[232,304,306,307,386,397,486,694,856] A similar pattern of response to OVAR can be obtained during constant velocity rotation about a vertical axis when combined with sinusoidal translation.[532] Because the changing orientation of the head with respect to gravity imposes a changing linear acceleration along the naso-occipital axis, not only is there the modulation component of slow-phase velocity, but also a sinusoidal modulation of the vergence angle as a function of head position with respect to gravity.[227] Bilateral lesions of vestibular nerve afferents abolish continuous nystagmus during OVAR.[187] Unilateral lesions lead to asymmetries in the modulation component.[451] Lesions of the nodulus affect the bias component of OVAR by virtue of its influence on the velocity-storage mechanism.[19,864] Patients with cerebellar ataxia may have an increased modulation component but an abnormal bias response.[11] Patients with brain stem lesions, too, may show different patterns of OVAR, with abnormalities in the bias component with caudal lesions and abnormalities in the modulation component with more rostral lesions.[811] Finally, age also has an effect on OVAR with a relative increase in the modulation component and relative decrease in the bias component.[304-306]

NEURAL SUBSTRATE FOR OPTOKINETIC RESPONSES

Both smooth pursuit and optokinetic systems contribute to the stabilization of images of stationary objects during head rotations. In humans, the optokinetic response to a full-field, moving visual stimulus has two stages: first, the prompt generation of nystagmus within 1 to 2 seconds of stimulus onset, with slow-phase velocity approximating stimulus velocity. This initial response mainly reflects smooth pursuit. Second, there is a slower buildup of "stored" neural activity. This activity is revealed as OKAN when the subject is placed in darkness.

In monkeys, vestibular nucleus neurons that respond to head rotation also are driven by optokinetic stimuli (Fig. 2–5).[395,848] Moreover, when the lights are turned off after a period of optokinetic stimulation, the vestibular nucleus neurons continue discharging for some seconds;[847] this is the neurophysiological correlate for OKAN. Vestibular nucleus neurons only respond well to low-frequency visual stimuli, in agreement with the demands made of the optokinetic system in replacing the r-VOR during sustained rotation.[119] Thus, during combined vestibular and optokinetic stimulation—which occurs during the natural situation of self-rotation—as the vestibular drive declines, the optokinetic input takes over and maintains a steady vestibular discharge that continues to generate compensatory eye movements (Fig. 2–5B). Thus the importance of testing OKAN is that it allows one to assay activity within the vestibular nuclei without employing any motion of the head. The neural substrate for OKN, and especially the nucleus of the optic tract (NOT) and accessory optic nuclei (AON), are discussed further in Chapter 4.

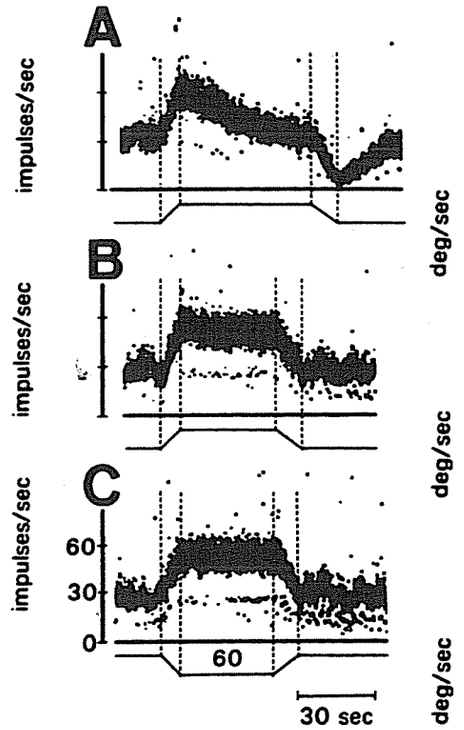

Figure 2–5. The response of a type I vestibular nucleus neuron of the alert rhesus monkey to vestibular and optokinetic stimulation. In each panel, instantaneous discharge rate (ordinate) is plotted against time (abscissa). Below each panel, the direction and magnitude of the stimulus is indicated (60 degrees per second). (A) The monkey is rotated in darkness. The initial vestibular response declines (to parallel the decline of per-rotatory nystagmus; see Figs. 1–4 and 2–7). (B) The monkey is rotated in the light. This time the neuron's response is sustained during the period of rotation. (C) The monkey sits stationary within a rotating optokinetic drum. This visual stimulus causes a sustained response of the same vestibular nucleus. (From Waespe and Henn,[848] with kind permission of Springer Science and Business Media.)

QUANTITATIVE ASPECTS OF THE VESTIBULAR-OPTOKINETIC SYSTEM

A quantitative description of any type of control system compares the output with a known input. Here we compare induced eye movements with head movements, using three important characteristics: (1) the ratio of amplitudes of the output and input (VOR gain); (2) the angle between the axis of head rotation and the axis of eye rotation (VOR direction); and (3) the temporal synchrony between the output and input (described by VOR phase or VOR time constant). We assume here that, to a first approximation, the VOR can be treated as a linear control system. In this case, transient and sinusoidal stimuli give rise to responses that are equivalent in terms of the mathematical information they reveal about the dynamic characteristics of a particular system. There are, however, important nonlinearities in the VOR, especially at high velocities, high accelerations, and at frequencies outside the usual range of natural head movements. These nonlinearities have important clinical and physiological implications.

Vestibulo-Ocular Reflex Gain, Direction, and Phase: General Characteristics

For the r-VOR, gain is given by the ratio of amplitude of eye rotation to amplitude of head rotation. For sine-wave stimuli (i.e., sinusoidal rotation of a subject in darkness, Fig. 2–6A), gain is usually calculated from peak slow-phase eye velocity/peak head velocity (Fig. 2–6B). The temporal difference between output and input is described by phase. Using sine-wave stimuli, the phase of eye and head movements may be compared (Fig. 2–6B); the difference (or phase shift) is expressed in degrees. For the frequencies of head rotation that correspond to most natural head rotations (0.5 cycles/second – 5.0 cycles/second), gain is close to 1.0 and phase shift is close to 180 degrees: equal-sized eye movements and head movements occur synchronously in opposite directions. By convention, the gain of the r-VOR that perfectly compensates for head rotations is assigned a value of 1.0, and the phase that perfectly compensates for head rotations is assigned a value of 0 degrees. For lower frequencies of rotation (less than 0.01 cycle/second), a shift in phase occurs and gain falls; this reflects the inability of the r-VOR to compensate for more sustained head rotations that contain low-frequency components. The ways that gain and phase change with different stimulus frequencies can be represented graphically, as a Bode plot (Fig. 2–6C).

Recent studies in the squirrel monkey have suggested that the phase and gain characteristics of the r-VOR can be best modeled with parallel linear (tonic) and nonlinear (phasic) pathways.[583] At higher frequencies of head rotation the gain of the r-VOR rises when velocity is above 20 degrees/second and this has been attributed to the actions of the nonlinear pathway. Likewise, the nonlinear pathway may mediate changes in the r-VOR for near viewing [575] and in adaptive changes in the r-VOR for higher frequency and higher velocity stimuli.[181,182,491,492,643] In the rhesus monkey, however, while there are also parallel phasic and tonic pathways, there is no evidence for a comparable nonlinearity to that of the squirrel monkey.[421] There is other evidence for parallel r-VOR pathways based upon studies of adaptation of the VOR.[681] The r-VOR in humans has also been modeled with parallel phasic and

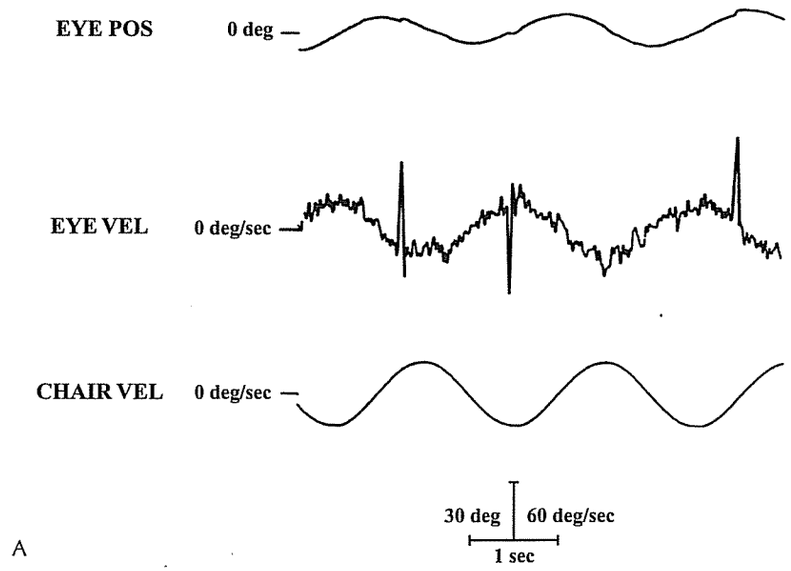

Figure 2–6. Quantitative evaluation of the vestibulo-ocular reflex using sinusoidal rotation in darkness. (A) A typical record of the VOR during sinusoidal rotation at 0.5 Hz. The subject is imagining the location of an earth-fixed target.

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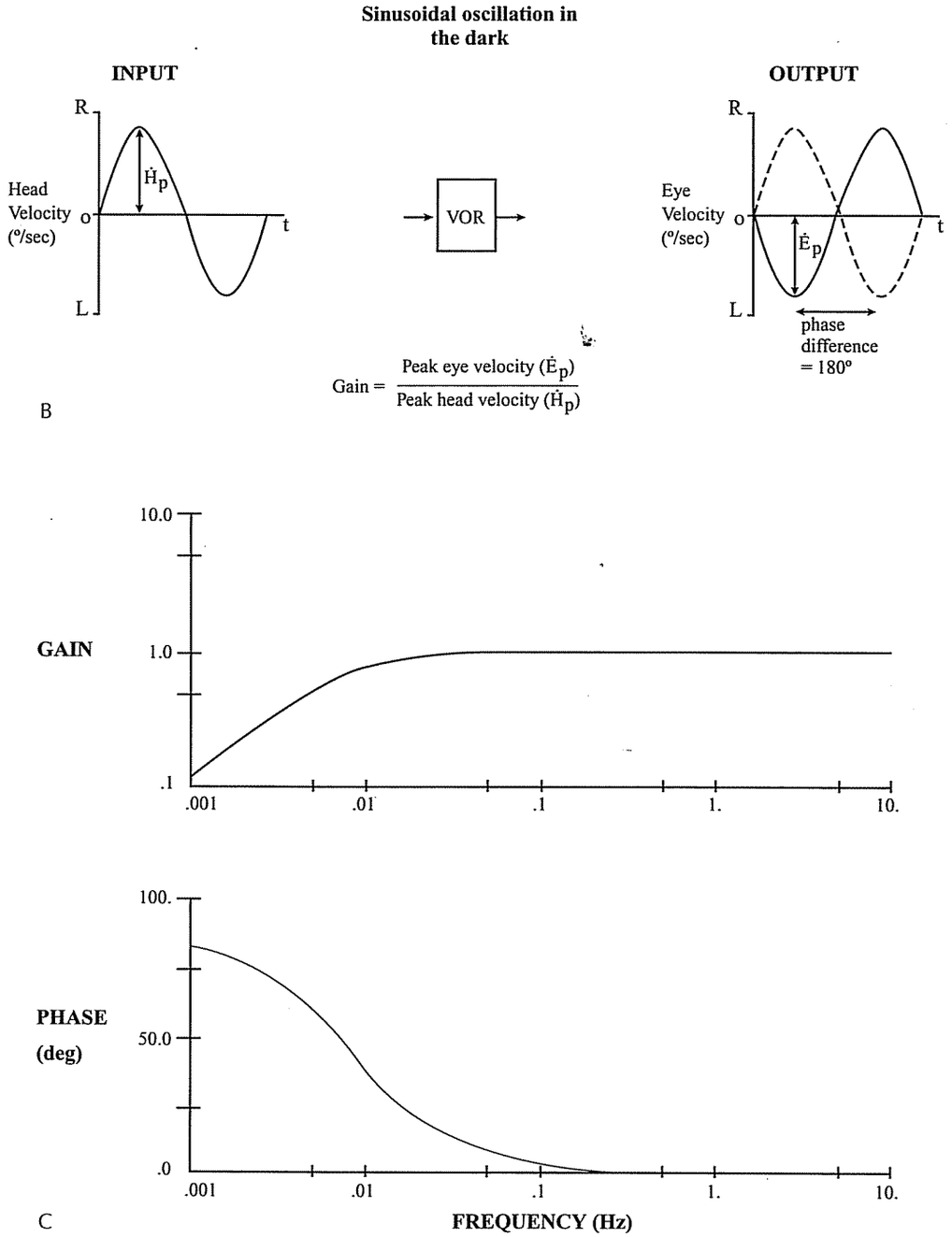

Figure 2–6. *(Continued)* (B) Schematic summary of vestibulo-ocular reflex during sinusoidal stimulation, as shown in (A). The graph on the left shows characteristics of the stimulus (head velocity) and the graph on the right shows the response (slow-phase eye velocity, quick-phases having been disregarded). R = right; L = left; t = time. In this case, vestibulo-ocular reflex gain is 1.0 and the phase difference between eye velocity and head velocity is 180° (by convention, this is referred to as "zero phase shift"). The dashed curve on the right represents head velocity. (C) A Bode diagram of the vestibulo-ocular reflex showing the idealized behavior of gain and phase with varying stimulus frequencies. Note that for the frequency range of most natural head rotations (0.5–5.0 Hz), gain is 1.0 and phase shift is zero degrees.

tonic pathways though the nature of any nonlinearity in the phasic pathway is as yet unclear.[493,643] An attractive, but not yet proven hypothesis is that the tonic (linear) and phasic (possibly with a nonlinearity) pathways correspond, at least in part, to the regular (tonic) and irregular (phasic) afferents, and to the type A and type B neurons within the vestibular nuclei, respectively (see above).

For sustained, constant velocity rotation (also called velocity steps or impulsive stimuli (i.e., an impulse of acceleration)), gain is usually calculated from initial eye velocity/head velocity. With such sustained rotations in darkness, vestibular eye movements (slow phases of nystagmus) progressively decline in velocity, and after about 30 to 45 seconds, the eye movements cease (see Fig. 1–6). The time course of the decline of slow-phase velocity is similar to a decaying exponential curve that can be defined by a time constant (Fig. 2–7). After one time constant, eye velocity has declined to 37% of its initial value; after three time constants, eye movements have nearly stopped. The time constant is mathematically related to the phase of the r-VOR observed during low-frequency sinusoidal stimulation: the larger the time constant, the less the dif-

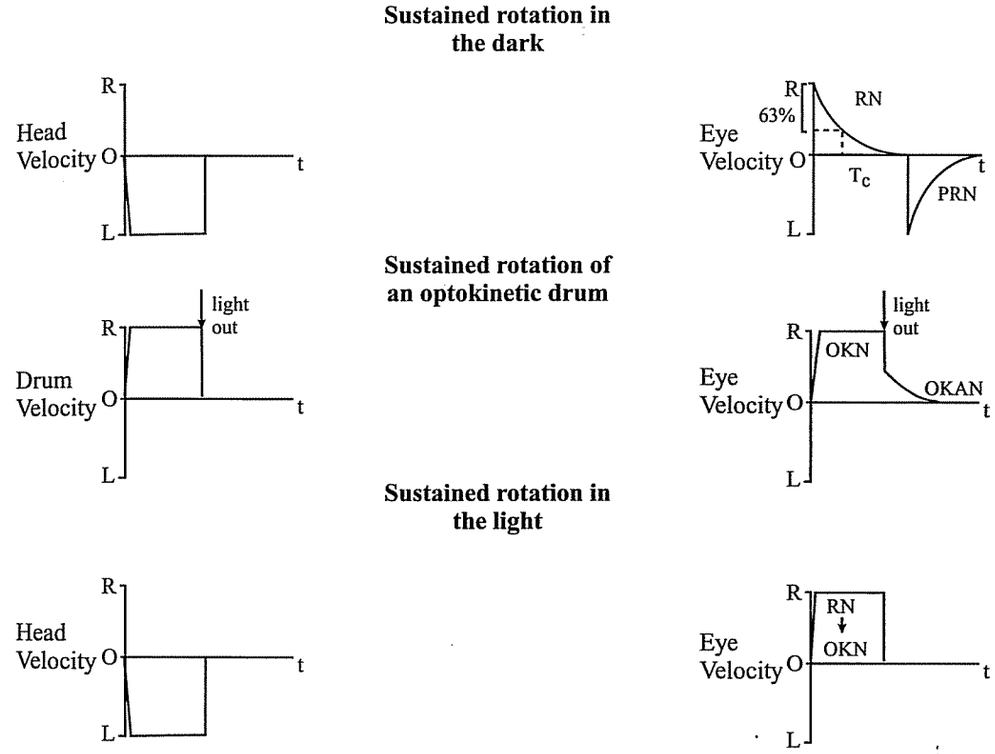

Figure 2–7. Schematic summary of vestibular-optokinetic interaction occurring in response to velocity-step ("impulsive" or constant velocity) rotations. Graphs on the left show characteristics of the stimulus (head velocity during rotation or drum velocity during optokinetic stimulation); graphs on the right show the responses (slow-phase eye velocity, quick-phases having been removed). R = right; L = left; t = time. In the top panel, constant-velocity rotation to the left in the dark produces slow-phase movements to the right (per-rotatory nystagmus, RN) with initial eye velocities equal to head velocity (VOR gain = 1.0). Slow-phase velocity subsequently declines. This decline may be approximated by a negative exponential with a time constant, T_C, given by the time taken for a 63% decline in eye velocity. When rotation stops, nystagmus starts in the opposite direction (post-rotatory nystagmus, PRN). In the middle panel, an optokinetic stimulus (drum rotation to the right) causes a sustained optokinetic nystagmus (OKN), with slow-phases to the right during the entire period of stimulation. When the lights are turned off during stimulation, eye movements do not stop immediately but persist as optokinetic after-nystagmus (OKAN). In the lower panel, the subject is rotated in the light (natural situation of self-rotation). This gives a combined vestibular and optokinetic stimulus. The response is a sustained nystagmus. When the chair stops rotating, eye movements stop nearly completely: post-rotatory nystagmus is suppressed by the oppositely directed optokinetic after-nystagmus and by visual fixation of the stationary world.

ference in phase between the head and eye at a given frequency and, hence, the better the compensation. The latency of the r-VOR is about 7 to 15 ms.

DETERMINANTS OF VESTIBULO-OCULAR REFLEX GAIN: ROTATIONAL VESTIBULO-OCULAR REFLEX

The gain and time constant of the human r-VOR are influenced by many factors, so normal ranges vary considerably. The torsional VOR, in response to roll rotation, has a lower mean gain value, typically 0.5, than the horizontal or vertical VOR to yaw or pitch rotations and can be influenced by the relative position of the roll axis and the gravity vector.[76,104,355,572,575a,658,658,720,721,735,736,819,821] The r-VOR measured in the light—the natural circumstance—may be more accurate (gain and axis of eye rotation) in the light than the dark, even at high frequencies of head rotation when visual following mechanisms are thought to be ineffective.[235,281,381,550]

During natural activities such as locomotion, the frequencies of rotational head perturbations may be greater than 5.0 Hz.[357] Measurements of the gain of the r-VOR with high frequency or brief, high acceleration stimuli have suggested that gain of the r-VOR is slightly less than 1.0 until frequencies of about 2 to 4 Hz and then rises to values of 1.0 or even higher at higher frequencies.[524,784] In response to transient stimuli the acceleration and velocity gains approach 1.0 early on, though there is a confounding effect of translation of the globe in the orbit, which may lead to a brief 'zero' latency anticompensatory response.[196] There is also a slight difference in latency between the two eyes with the adducting eye lagging the abducting eye by about 1 ms. This difference presumably reflects the presence of an extra neuron (the abducens internuclear neuron) in the pathway to the medial rectus.

Target Proximity

One important factor is that the gain of the VOR during head motion is affected by the proximity of the target (or imagined target) of interest. During viewing of a near target, the brain must compensate not only for the rotation of the head but also for the lateral or vertical displacement (translation) of the orbits (Fig. 7–7, Chapter 7). Consequently, the gain of the VOR for yaw or pitch axis rotation increases during viewing of a near object.[200,202,381,405,572,575,638,836] The perception of distance may be more important than the fixation distance based on vergence angle or on the actual target distance itself;[179,381,747] this is another piece of evidence for the relatively strong influence of higher-level cognitive control of adjustment of the gain of the t-VOR for translation of the head.[682] The exception to an adjustment for near viewing is the gain of the roll VOR, which elicits torsion and hence requires no change for near viewing. In fact, as discussed previously, there is some evidence that the gain of the roll VOR decreases at near to eliminate problems related to potential vertical misalignment of the eyes.[84,243a,443,572]

Mental Set

A second important determinant of the gain of the VOR, particularly when measured during rotation in darkness, is the mental set or imagined percept that the subject chooses during rotation.[74,381,446,590,591,638] If the subject imagines fixation of an earth-fixed visual scene during low-amplitude and low-frequency sinusoidal rotation, the gain of the r-VOR increases to approximately 1.0. On the other hand, if the subject imagines a visual stimulus that moves with the head, then the gain of the r-VOR declines to about 0.1. Finally, if the subject makes no attempt to imagine a visual stimulus but is distracted by performing mental arithmetic, the gain of the r-VOR is intermediate between these two extremes.[74] This voluntary control of the gain of the r-VOR is most effective during lower-frequency head rotations. If the subject daydreams or closes the eyes, the gain of the r-VOR is variable and low; thus it is important to keep the subject alert, such as by asking the subject to vocalize during vestibular testing.[536,872]

Active Versus Passive Head Rotation

While the passively induced r-VOR is close to compensatory over a relatively wide range of frequencies and velocities, active head rotations around the pitch and yaw axes still lead to a more faithful response, taking into account viewing distance and the different needs of both eyes related to translation of the orbits relative to the point of regard.[96,550] On the other hand, active head rotation around the roll axis still leads to an undercompensatory torsional VOR response. This might be due to a relative lack of exposure to pure roll rotations during natural behavior, the relative unimportance of torsional retinal slip in the retinal periphery, and the need to prevent vertical misalignment during rotation in roll when the eyes are converged.[586] The gain of the r-VOR is also enhanced by a prior eye movement,[234] light, *per se*,[235] and by predictive mechanisms during sinusoidal rotation.[381,877] Clearly, many factors can confound the interpretation of whether or not the gain of the VOR in a given subject under a given set of circumstances is normal.

Changes with Age

The VOR also changes with age. The elderly show a decrease in gain, predominantly at low frequencies of stimulation and high speeds of rotation. This is associated with increasing phase lead (i.e., a lower r-VOR time constant).[57,65,631,659,660] These changes in the r-VOR are probably related to the senescence of the velocity-storage mechanism and age-related loss of neurons within the vestibular system.[518,791] There are also age-related changes in OVAR.[304] Higher gains of the r-VOR have been reported in normal children, though OKN gains were equivalent to those for adults.[712] With head impulses in the elderly there are also changes in the r-VOR; initially the response is normal but it fades quickly.[800]

DETERMINANTS OF VESTIBULO-OCULAR REFLEX GAIN: TRANSLATIONAL VESTIBULO-OCULAR REFLEX

A number of investigators have measured the t-VOR response of human subjects to lateral motion.[49,67,144,203,323,324,638,682,683,728,750] The results are largely in accord with findings in monkeys.[28,547,577,639,640,728,794] All studies show that compensatory slow phases are a linear function of the reciprocal of the viewing distance, though humans tend to have a lower gain than monkeys (i.e., the movements are not truly compensatory). One possible explanation for the difference in the gain between the two species is that the various cues used to estimate the distance of the target of interest are weighted differently by monkeys and humans. Vergence and accommodation may be relatively more important for monkeys; size and other cognitive cues to distance may be more important for humans.[54,154,179,201,747,794,870] Another reason for an undercompensatory response of the human t-VOR is that the compensatory response to a given head translation depends critically upon the relationship of the position of the eyes in the orbit relative to the location and motion of the target relative to the head (see below). For example, during surge (fore and aft) translations the eye movement response is very different depending upon whether one is looking straight ahead (when vergence is called for) or when one is looking eccentrically (when there must be a large, nearly conjugate, horizontal or vertical component). Thus, it may be advantageous to keep the baseline t-VOR relatively low so the reflex can be adjusted up or down more easily depending upon viewing requirements.[682,683] Vergence cues may also be more important for adjusting the t-VOR gain for distance when the frequency of the stimulus is higher.[635,794] Mental set and context probably play important roles in "preparing" the anticipated response to head translation.[682] Indeed without the knowledge of whether the fixation point is going to be head fixed or space fixed, the t-VOR behaves differently than with the usual space-fixed target in which the t-VOR is traditionally tested. Because of the general undercompensatory nature of the t-VOR saccades become an important part of the response, being triggered automatically and scaling in a similar way to the slow-phase response. Thus, as is the case for the r-VOR when it is made undercompensatory by disease, the vestibular system uses the full ocular motor repertoire in the attempt to optimize vision during head motion. Finally, the gain of the actively generated t-VOR is much closer to ideal than is the response to passive translations, even in normal subjects.[549]

Influences of Direction of Gaze

As indicated above the response of the t-VOR critically depends on where the eyes are pointing (i.e., their positions in the orbit). The correct axis of eye rotation for a given direction of head translation must be calculated, so, for

example, during naso-occipital motion, if the eyes are pointing upward, a vertical eye rotation is called for, but if the eyes are pointing to the side a horizontal eye rotation is called for. Depending upon whether gaze is up or down, or right or left, the direction of the eye movement will reverse. In addition, disconjugate eye movements may be needed (for example, during horizontal translation when the target of interest is off to the side), and even disjunctive eye movements—convergence and divergence—are required during naso-occipital translation when looking straight ahead.[547,639,684,765,803,813] The latency of the t-VOR in humans may be influenced by mental set, context, and viewing distance, especially at lower frequencies. For abrupt, high acceleration stimuli the latency is less than 20 ms.[682,683] The compensatory responses to vertical (bob, up-down) linear accelerations are subject to viewing distance in a way similar to the horizontal t-VOR.[634] In monkeys, the latencies of the vertical and horizontal t-VOR are about 12 to 18 ms.[25,155,728]

Several important questions about how otolith signals are processed to produce responses to linear acceleration are unanswered. First, the brain must distinguish linear acceleration associated with lateral tilt of the head, which calls for a static change in torsion or ocular counterroll, from linear acceleration associated with translation of the head, which calls for horizontal (to interaural translation) or vertical (to dorsal-ventral translation) slow phases. Inappropriate torsion occurs during interaural translation,[509] especially at low frequencies of translation.[794] Thus, the frequency of the stimulus may be one important cue, because in natural circumstances, relatively high-frequency stimulation of the otoliths is usually associated with translation, and relatively low-frequency stimulation with head tilt.[20,637,640,794] A model incorporating this idea is presented in Figure 2–8. There are other important factors, however. The static orientation of the head relative to gravity, on which an additional (translational) linear acceleration is imposed, can also influence whether inappropriate torsion occurs in response to translation, and whether it is conjugate.[558,561,562]

Recent work, using both intact and canal-plugged animals, with patterns of canal and otolith stimulation (roll-tilt and translation) that allow one to isolate the canal and otolith inputs to the t-VOR, has emphasized the importance of contextual cues from simultaneous semicircular canal activation during otolith stimulation.[26,344] For example, the activation of the vertical canals in association with activation of the otoliths during lateral head tilt and not in association with activation of the otoliths

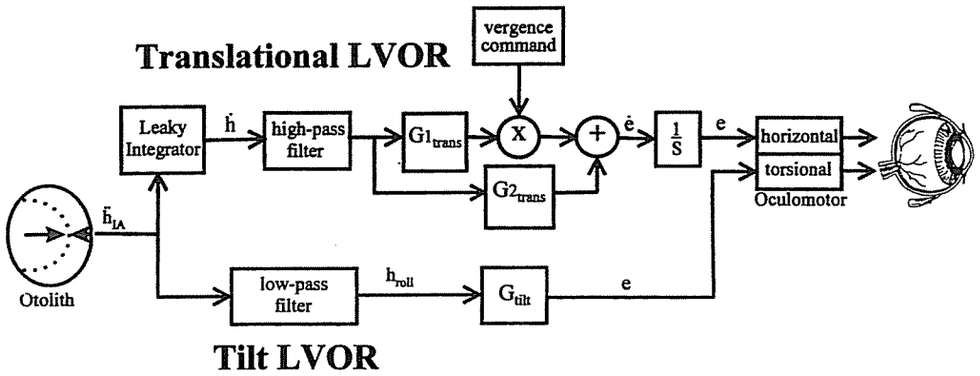

Figure 2–8. A model of the translational vestibulo-ocular reflex for lateral (IA, interaural) head acceleration. Pathways for the L-VOR (linear VOR) are shown. The tilt pathway contains a low-pass filter and scaling (G_{tilt}) to produce ocular counterroll. The translational pathway includes a mathematical integration (acceleration-to-velocity) and a high-pass filter before splitting into two subpathways, one with a gain element ($G2_{trans}$) that accounts for the response at zero vergence (an offset term, since theoretically no t-VOR is required when viewing is at optical infinity and vergence is zero), and another with a gain element ($G1_{trans}$) and a multiplier by which a "vergence command" signal is used to modulate response amplitude (which accounts for the slope of t-VOR gain as a function of vergence (i.e., viewing distance)). The summed output of these two subpathways (which is a velocity signal) is passed to a second integrator (the classic velocity-to-position integrator for conjugate eye movements) that generates the signal to control eye position. S is the Laplace transform operator. (Reproduced with permission of the American Physiological Society from Telford, Seidman, and Paige.[794])

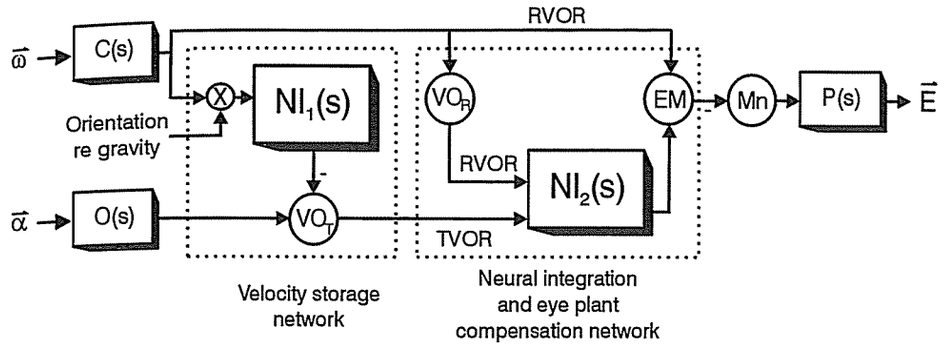

Figure 2–9. A model of the vestibulo-ocular reflex using an orientation detector based upon signals from the semicircular canals to resolve tilt and translation. Inputs to the model are angular head velocity $\{\vec{\omega}\}$, sensed by the semicircular canals C(s) and linear acceleration $\{\vec{\alpha}\}$, sensed by the otolith organs O(s). Output of the model is eye position $\vec{E}$. Boxes in the schematic are dynamic elements that represent either a sensor [C(s) and O(s)], the motor plant [P(s)], or a neural filtering process [$NI_1(s)$, $NI_2(s)$]. Two central filtering processes include the "oculomotor integrator" [$NI_1(s)$] and an integrative network for the canal signals [$NI_1(s)$] that could be the velocity-storage integrator. Circles are summing junctions used to represent particular cell populations including vestibular-only (VO) cells, VO_r and VO_t, that mediate sensory signal flow in the RVOR and TVOR pathways, respectively, premotor eye-movement-sensitive (EM) neurons and motoneurons (Mn). Circle labeled with an X in the schematic indicates a proposed head-orientation-dependent modulation in the coupling between semicircular canal sensory signals and the integrative network NI_1. (Reproduced with permission from Green and Angelaki with permission of the American Physiological Society.[345])

during translation can help the brain to distinguish head translation from tilt.[14,26,34,35,345,911]

Based upon the above observations several groups have proposed new models for the organization of the central neural circuits underlying the generation of the t-VOR.[16,30,34,35,344-346,564-566,599,637,743a,911] One new idea relates to the processing of otolith signals by central vestibular pathways, and the other idea to distinguishing tilt from translation. These ideas are summarized in a recent model of the generation of the r-VOR and t-VOR (Fig. 2–9).[13,345]

There are two key points. First, at least in part, otolith and canal signals are processed differently within central vestibular pathways. While both are integrated centrally to produce an eye position signal, the canal signals have a strong direct projection to ocular motor neurons (which compensates for the filtering properties of the ocular motor plant), while otolith signals have a weaker direct projection to the ocular motor neurons so that at high frequencies of stimulation a second integration is provided by the ocular motor plant. These two integrations allow the t-VOR to transform the original otolith signals conveying information about linear acceleration into the appropriate position-coded signals for the eyes to compensate for head motion. The second point relates to how tilt and translation are distinguished. The crucial circuit here is an orientation network into which both canal and otolith signals project. They are then multiplied and integrated by a head velocity to head position integrator. The output of the integrator within this orientation network is then compared—possibly on vestibular only (VO) cells—with the net gravitoinertial acceleration as detected by the otoliths. Using these two signals the vestibular system can compute an internal estimate of head translation, which then drives the t-VOR. This model has many attractive features and the behavior of a number of neurons within the brain stem and cerebellum (including the fastigial nuclei) fit the requirements of the model.[34,345,743]

The following issues are still to be sorted out:

1. The effects of stimulation of the medial versus lateral portions of the utricle on which compensatory response is elicited, tilt or translation
2. The relative importance of the primary and of the polysynaptic projections of otolith-ocular reflexes
3. The possible role of irregular versus regular otolith afferents in distinguishing tilt from translation
4. The specific circuits that mediate

responses to tilt (which induces counterroll and must activate the vertical rectus and oblique muscles) and translation (which requires horizontal eye motion and must activate the horizontal rectus muscles)

5. The specific circuits that calculate and implement the necessary adjustments to the t-VOR response based upon the location of the eyes in the orbit relative to the direction of translation of the head.

Another issue relates to the role of the smooth pursuit system in the generation of the t-VOR.[54,144,638,752] Recall that functionally, pursuit and the t-VOR are complementary in the same way as OKN and the r-VOR. It may be that pursuit plays some role in generating the slow phases in response to low-frequency translations; the usual response to a natural low-frequency linear acceleration (tilt of the head) is ocular counterroll. High-frequency responses to linear acceleration (translation) probably occur independently of pursuit, as is the case for the r-VOR during high frequencies of head rotation.

DETERMINANTS OF VESTIBULO-OCULAR REFLEX GAIN: ECCENTRIC ROTATION

Transient responses to linear acceleration have also been investigated using a paradigm in which the axis of head rotation is placed eccentrically, combining linear and angular components. Both the viewing distance and the location of the axis of rotation relative to the orbits must be taken into account. Results in monkeys[561,639,766-768,836] are similar to those in humans.[10,201,208,561,738]

Studies in the monkey of the compensatory response to an abrupt rotation, with the head positioned eccentrically to the axis of rotation, have shown three sequential adjustments for viewing distance and the linear motion of the orbits that follow the initial response.[767] The first 20 ms of the slow-phase response is independent of viewing distance and the location of the rotation axis. In the next 20 ms, an adjustment is made for viewing distance. The next adjustment is for translation of the otoliths and occurs within 30 ms. The final adjustment—within 100 ms—is for eye translation relative to the visual target and compensates for the difference in the relative anatomic locations of the otoliths and the orbits. Coincident with these adjustments is an imposed disconjugacy of the VOR, which does not become evident until at least 10 ms after the VOR has begun. The adjustment of the VOR for vergence angle appears to be on the basis of an efference copy signal of vergence or some other internal measure of target distance, since the change in r-VOR anticipates the vergence change by about 50 ms.[768] The substrate for the modulation of the r-VOR during eccentric rotation may be, at least in part, in the flocculus of the cerebellum.[766] Patients with cerebellar disease also have difficulty adjusting the r-VOR for near viewing.[205]

In humans, the pattern of response to eccentric rotation appears roughly similar,[208,738] though recent work has emphasized the importance of cognitive set and prior knowledge of to where the line of sight must point.[682] In the first 40 ms after the onset of rotation there is an adjustment for target distance that is independent of translation. In the next 60 ms, an otolith-related adjustment (relative to target distance and the eccentricity of the head from the axis of rotation), appears and eventually masks the initial canal-related adjustment. The VOR during eccentric rotation is also adjusted during sinusoidal rotation.[207,351,738,838]

How are the various signals from the labyrinth during eccentric rotation combined centrally? In the monkey, the interaction between the angular and the linear VOR has been studied using combinations of linear and angular accelerations, at different frequencies, amplitudes, and head orientations.[637,792,793] By placing the head in front of or behind the center of rotation, the t-VOR can be made to add or subtract from the r-VOR. Overall, these data are compatible with the idea that the VOR during eccentric rotation is accounted for by summation of the isolated response to a comparable pure translation stimulus on a linear sled, and the isolated response to rotation with the head centered on the axis of rotation.

In humans, the linear and angular components of the VOR during eccentric rotation interact in a similar way, though there is some disagreement as to how well the interactions can be accounted for by simple summation of the t-VOR and r-VOR. In one study, the linear response associated with rotation was reported to be higher than would be predicted from simple linear summation of the t-VOR induced during pure translation and the r-VOR induced during head-centered rotation.[10] Likewise, the response to stimulation of the semicircular canals may inappropriately dominate the linear response and the effect of viewing distance.[145] In other studies of eccentric rotation during yaw (horizontal) and pitch (vertical) rotation, a linear model of canal and otolith interaction could account for the findings.[199,199,637,738] The specifics of the neuronal processing underlying these canal-otolith interactions remain to be demonstrated. As discussed above several models have been presented recently that emphasize building an internal model of head orientation using signals from the otoliths and the concomitant excitation of the semicircular canals to determine whether linear acceleration signals reflect tilt or translation.[34,73,563,692,694,911]

DETERMINANTS OF VESTIBULO-OCULAR REFLEX GAIN: DIRECTION AND THE AXIS OF EYE ROTATION

The direction of the r-VOR is determined by the angle between the axes of head and eye rotation. Not only must the amplitude of the VOR be equal (and opposite) to that of head rotation, but the axis of eye rotation must be parallel to that of head rotation. If this is not the case, there will be a misalignment of the axes around which the eyes and head rotate leading to inappropriately directed slow-phase eye movements. In the past this has been called "perverted" nystagmus when, for example, caloric stimulation or horizontal head-shaking elicits a vertical nystagmus.[579,815] Such vestibular axis shifts arise in several circumstances. One example is when the VOR produces a normal amplitude and correctly directed response along the axis of stimulation but with an additional inappropriately directed component (e.g., a vertical component during yaw axis rotation). Another example is when the gain of one component of the VOR is different from that of the other during a rotation of the head around an axis that calls for two compensatory responses (e.g., a mixed vertical-torsional response during rotation around an axis perpendicular to the coplanar vertical canals on each side, for example, right anterior—left posterior (RALP), or left anterior—right posterior (LARP)). The gain of the torsional VOR is normally less than the gains of the vertical and horizontal VOR, so rotation of the head around any axis that calls for a mixed vertical-torsional or mixed horizontal-torsional response will lead to misalignment of the axes of head and eye rotation.[48,384,572,587,770,821]

Another source of axis misalignment for the horizontal and vertical VOR occurs when the position of the eye is moved in a direction orthogonal to the plane of eye rotation (e.g., positioning the eye up or down and then measuring the horizontal VOR for rotation around the yaw axis). If the axis of eye rotation remains head-fixed (and does not obey Listing's law—see Chapter 9) there should be no axis shift. Indeed this non-Listing's law strategy is optimal for the r-VOR as one would want the eye to rotate around an axis exactly parallel to that of the axis around which the head is rotating. If Listing's law is obeyed, however, there will be a torsional eye velocity component that, in the case of the horizontal VOR, is related to the degree of vertical eccentricity in the orbit, or in the case of the vertical VOR, to the degree of horizontal eccentricity in the orbit. The amount is dictated by the so-called half-angle rule for Listing's Law (the axis tilts by half the angle of eccentricity). The r-VOR actually obeys approximately a quarter-angle rule (producing a small amount of axis misalignment) though during the initiation of the VOR during rapid head impulses there is controversy as to whether or not the axis of eye rotation changes as the head rotation continues.[204,644,799,802]

Axis shifts also occur during sustained head rotations (i.e., low-frequency stimuli), and relate to the velocity-storage mechanism and the orientation of head with respect to gravity.[692] The cerebellar nodulus plays a key role in determining the axis shifts related to the velocity-storage mechanism.[189]

For the t-VOR, slightly more than the half-angle rule is obeyed (which is close to obeying Listing's law and similar to that of pursuit or saccades), as would be expected from a reflex that primarily serves the needs of foveal stabilization and binocular vision.[36,587,642,850] Another important determinant of the axis of eye rotation during the t-VOR is the location of the target of interest relative to the head (i.e., eye position in the orbit). For example, during surge (fore and aft) translations of the head, if the eyes are looking up, rotation around the pitch axis is desired; if looking laterally, rotation around the yaw axis; if looking straight

ahead, a vergence movement is required. Because the calculation of the correct axis of eye rotation during translation of the head is so complex, one might expect that inappropriately directed eye movements during head translation would be common in both peripheral and central vestibular disorders. This may be true but has been looked at only in a few circumstances, with cerebellar lesions and after experimental unilateral labyrinthectomy, for example.[633,901]

One other issue related to the function of the VOR and Listing's plane is how the eyes get back into Listing's plane after a torsional slow-phase response to roll VOR or roll OKN stimulation. One strategy, of course, is to keep the gain of the torsional VOR relatively low, and this is the case.[586] Vestibular-induced saccades (i.e., quick phases) also help reset the torsional orientation of the eyes.[494,572,820]

Axis shifts become even more complicated with near viewing because Listing's plane undergoes a temporal shift when the eyes converge.[528,573,585] Another source of axis shift and disconjugacy in the horizontal VOR may relate to the changes in the position of the horizontal rectus connective tissues pulleys within the orbit. These pulleys determine the axis of eye rotation and they may change their positions on up and down gaze.[244] Pulley shifts also occur during static ocular counter-rolling and alter the pulling directions of the vertical torsional muscles.[243a]Axis shifts commonly occur with unilateral peripheral lesions[40,164,209,211,212] and with central, and especially cerebellar, lesions. In the latter there often is an inappropriately directed upward component during yaw axis rotation, which may also be different in the two eyes.[852,853,901] This 'cross-axis' abnormality has been attributed to 1) a loss of normal cerebellar inhibition on anterior canal VOR pathways and 2) a loss of the mechanism that adjusts for the differences in pulling directions of the oblique and rectus muscles that are innervated by the primary connections of the VOR.

DETERMINANTS OF VESTIBULO-OCULAR REFLEX PHASE AND TIME CONSTANT

The time constant of the human r-VOR, using velocity-step rotations, shows considerable inter-subject variation, with a range typically between 10 and 15 seconds.[61,185,659] As indicated above, these values are greater than predicted from the mechanical properties of the semicircular canals. Thus, the nystagmus outlasts the duration of the signal recorded from the vestibular nerve. The difference represents a prolongation or perseveration of the raw vestibular signal by the brain, and is accomplished by the velocity-storage mechanism. Factors that may cause the time constant of the r-VOR to decline include repeated testing (habituation),[4,59] peripheral vestibular disease,[136,279] and visual deprivation in early life.[754] Newborn babies have a time constant of the VOR that is about 6 seconds, but adult values are attained during the first few months of life. This change probably reflects maturation of visual pathways, which are important for calibration of the VOR, including the development of velocity storage.[756,873]

Static head position can also influence the time constant of the r-VOR though these effects are weaker in humans than in monkeys. Tilting of the head, forward or laterally, immediately following a head rotation, reduces the duration of post-rotational nystagmus, probably by disengaging or dumping activity in the velocity-storage mechanism.[105,189,282,283,692] During rotation around an earth-vertical axis, if the head is held in a tilted position, the time constant of the r-VOR measured in the earth-horizontal plane decreases in proportion to the degree of head tilt. The compensatory response has both horizontal and vertical components of rotation with respect to the orbit. The time constant of the two components may differ, leading to a change in the axis of eye rotation.[363,819]

Vertical vestibular responses may be asymmetric, often (but not always) favoring upward rather than downward slow phases.[55,56,107,468,535,819] Some of these asymmetries probably arise in the vertical velocity-storage mechanism (although this is relatively weak compared to the horizontal r-VOR), so they may appear or change direction during low-frequency stimulation (the later part of a constant-velocity rotation).[140,385,819,821] Circularvection—an illusory sensation of self motion induced by purely visual inputs—also shows an up-down asymmetry during pitch optokinetic stimulation.[311] In monkeys and cats, there is a spontaneous downbeat nystagmus in darkness; it may increase as the head is tilted away from the upright.[709] In humans, there is commonly a vertical drift in the dark, too, though in the head-upright position, it can be either up or down.[334] When the head is placed prone, an upward bias is added to the spontaneous drift present in the upright position. In the upside-down position normal subjects have a 'chin-beating' nystagmus.[466] These findings may be related to biases in the processing of information from the saccules (which are optimized to detect up-down linear acceleration of the head). Clinically, pathologic vertical nystagmus is more commonly down-beating, perhaps because of an inherent upward bias in the otolith system. Alternatively, there may be an inherent upward bias in canal pathways mediating the vertical r-VOR, either at a peripheral or central level,[111,433] though asymmetries in vestibulocerebellar pathways may also lead to an upward slow-phase bias.[531,665] The pathogenesis of downbeat nystagmus is discussed further in Chapter 10.

The time constant of the torsional VOR during rotation about an earth-vertical axis, with the subject's face supine or prone, is typically 4 to 5 seconds, suggesting that there is little velocity storage for the roll VOR.[735,819]

To sum up, the amplitude and direction of compensatory VOR responses around all three axes of rotation must be adjusted according to the rotational and translational components of the head movement, the point of regard (i.e., the target of interest), the position of the eye in the orbit, and a knowledge of the anatomic locations of the otolith organs relative to both orbits. Finally, any imposed linear acceleration must be separated into its gravitational and translational components. In addition, a number of cognitive factors come into play, depending upon context and anticipation. Thus, the VOR is subject to a variety of influences, making it a far more complicated reflex than previously thought.

Optokinetic Nystagmus

Optokinetic stimulation occurs naturally during sustained self-rotation in the light. In the laboratory, the optokinetic system is usually stimulated by rotating a large patterned drum around the stationary subject. The subject experiences a compelling sensation of self-rotation called *circularvection*, even though there is no peripheral vestibular stimulation.[77,125,569] During optokinetic stimulation in humans (e.g., the drum rotating at 60 degrees per second for 60 seconds, see Fig. 2–7), both the smooth pursuit and optokinetic systems contribute to this response. The ocular-following reflex—a rapid full-field visual following response that is closely allied to the mechanisms generating smooth pursuit—also contributes to the early phase of optokinetic tracking.[790] At the onset of the stimulus, the smooth pursuit system is most important and causes eye velocity to reach its maximum within a second or two. Typically, for stimulus velocities less than 60 degrees per second, the gain (eye velocity/stimulus velocity) is about 0.8.[66,288,831] Vertical optokinetic responses tend to be of lower gain than horizontal responses, and most subjects show a greater gain for upward stimulus motion than for downward.[107,317,535,595] A number of possibilities might explain this difference including asymmetry in otolith (saccular) inputs, vertical semicircular canal inputs, and central processing of up and down slow-phase eye movements.[665] If the subject actively looks at the moving stimulus, greater eye velocities can be achieved than if the subject passively stares at the surround. This difference may represent greater activation of smooth pursuit during the former condition. The luminance of the target is also an important factor.[859] Attention to the stimulus may be as important as the area of retina being stimulated in determining the optokinetic response.[1,1a,156,173] The gain of vertical optokinetic nystagmus (OKN) is influenced by binocular disparity. This finding supports the view that the optokinetic response is optimized for viewing of objects in the plane of regard.[416,576] The effects of attention and prediction on visual tracking are discussed further in Chapter 4. Like pursuit, OKN gain declines with age, due to a loss at both high frequencies and high velocities.[287,630] Curiously, circularvection may become enhanced with age, perhaps reflecting greater dependence on visual cues for orientation in the elderly, as labyrinthine and proprioceptive sensations become blunted.[631]

Torsional OKN can be induced by a roll stimulus. For example, watching a revolving disk directly in front of oneself elicits such a response. The gain and range of torsional OKN responses are low and depend upon size of field, speed, and disparity.[174,175,197,272,417,

[424,593,843,860] Torsional OKN may be asymmetrical in unilateral vestibular loss, showing a better response when the torsional slow phases are such that the top pole rotates toward the impaired side.[517]

Optokinetic After-Nystagmus

An important property of the optokinetic system is a persistence of the response after the stimulus has ceased. During the stimulation period, the optokinetic system effectively acts through the velocity-storage mechanism. After the lights are turned out, nystagmus continues in the same direction for some seconds, with a declining slow-phase velocity; this is called optokinetic after-nystagmus (OKAN). The velocity-storage mechanism that causes OKAN is probably the same one that causes the time constant of the r-VOR to be 2 to 3 times greater than the time constant of the cupula of the semicircular canals.

As can be seen in Figure 2–7, the optokinetic and vestibular systems temporally complement each other during and following sustained rotation in the light. Thus, during rotation, as the r-VOR declines, optokinetic responses, supplemented by the pursuit system, take over. When the period of self-rotation ends, OKAN is a mechanism by which post-rotational nystagmus can be counteracted.[75] Overall, however, in foveate animals, visual fixation (and smooth pursuit) are more important in nullifying post-rotational nystagmus.

In humans and monkeys, the properties of the optokinetic system can only be separated from those of smooth pursuit by studying OKAN. Four separate measures of OKAN are initial eye velocity, time constant of slow-phase decline, cumulative slow-phase eye position, and symmetry. If all lights are turned out after a period of optokinetic stimulation (e.g., 60 degrees per second or 150 degrees per second for 60 seconds), initial eye velocity reflects the persisting action of smooth pursuit, but this is largely gone within a second, and subsequently the initial value of OKAN can be measured. (Typically it is 10 degrees per second.)[734,808] Maximal amounts of OKAN are produced by relatively large values of retinal slip, in the range of 30 to 100 degrees per second.[288] By measuring the rate of decline of slow-phase velocity, and fitting this with a negative exponential curve, the time constant of OKAN can be determined; reported values range considerably, from 5 seconds to nearly 50 seconds. [288,488,734,808] Cumulative slow-phase eye position (the sum in degrees of all the slow phases) is another, less variable measure of OKAN.[368] Most normal subjects show less than a 6 degrees per second difference between rightward and leftward initial OKAN velocities.

Because of considerable intra-subject variability in measurements of initial OKAN eye velocity and time constant, it is necessary to make as many as a dozen separate measurements to obtain reliable results.[808] One way of achieving this, and avoiding prolonged and tedious testing, is to monitor the buildup of slow-phase velocity of OKAN during stimulation, by briefly turning out the lights at intervals.[734] This procedure is detailed further in the section below.

Optokinetic after-nystagmus declines with age.[757] OKAN may be more prominent in women.[808] With the head upright, OKAN in the vertical plane is usually absent and, when present, only occurs following upward stimulus motion.[107,502,535,595] These asymmetries are affected by head tilt[198] and space flight.[177,180] They are also modified in the altered-gravity period during parabolic flight, implicating otolith (saccule) inputs in their genesis.[177,867] There are asymmetries in the illusions of motion in response to vertically moving optokinetic stimuli that correspond to asymmetries in vertical optokinetic eye movement responses.[520] Similar to vestibular testing, repeated optokinetic stimulation can lead to reduced duration of OKAN.[444] Tilting the head forward, backward, or laterally shortens the duration of OKAN, an effect similar to that of head tilt on post-rotational nystagmus.[868] Fixation of a small, stationary target during optokinetic stimulation suppresses subsequent OKAN,[125,288] though a reversal phase of OKAN may appear if the period of stimulation is relatively long.[484] On the other hand, a brief period of fixation of a stationary target following optokinetic stimulation has little effect on OKAN.[288] These results suggest that fixation of a small target may act to "switch off" visual inputs to the velocity-storage mechanism, but once the mechanism is "charged", fixation has little influence on the course of OKAN.

Cervico-Ocular Reflex

The cervico-ocular reflex (COR), when tested in darkness using rotation of the body underneath the stationary head, has a low gain at frequencies corresponding to most natural head rotations for normal human subjects.[448,716,723] Only in some infants may a higher gain be seen,[458,697] and the gain may increase again in old age.[462] If labyrinthine function is lost due to disease, however, the COR may increase in gain and assume greater importance in generating compensatory eye rotations during natural head movements.[148,148,393,458,723] In patients with bilateral loss of vestibular function, isolated stimulation of cervical afferents during body rotation produces both slow phases and catch-up saccades in the same direction (i.e., opposite to relative head motion) to aid gaze stabilization (see Table 7–1). If labyrinthine function recovers, the cervico-ocular reflex may revert to its previous low gain.[147] In labyrinthine-defective patients, and even in normal subjects, the COR can be enhanced when subjects are instructed to attempt to fix upon a part of their trunk that is moving relative to the stationary head, rather than just to keep their eyes focused on a stationary position in space.[423] The latter instruction could act to cancel compensatory slow phases, unless there was a perception of the head moving in space. The COR can be actively trained in labyrinthine-deficient patients using magnifying and reducing lenses in a similar way to adaptation of the gain of the r-VOR.[423] Indeed adaptive changes in the COR can be induced in normal subjects.[698] Again, the mental set and the perception of the subject of the context in which the neck afferents are being stimulated are critical in determining whether the COR should be enhanced (if the head is perceived to be moving) or decreased (if the head is perceived to be still).[393,729] Cervico-ocular reflexes contribute little to ocular counterroll (with lateral tilt of the head relative to the body) in normal subjects, but in patients with bilateral labyrinthine loss, their contribution can be considerable.[101,458,666] Patients with bilateral labyrinthine loss and coincident cerebellar disease may not show enhancement of the COR, suggesting a role for the cerebellum in this aspect of vestibular adaptation.[148] Cervical afferents may influence the velocity-storage mechanism; OKAN is made asymmetric during optokinetic stimulation with the head kept turned relative to the body.[456] The COR is mediated by the same neurons in the vestibular nuclei that underlie the VOR, and the flocculus, too, may influence the COR.[321,322] The issue of cervical vertigo is discussed in Chapter 11.[122]

ADAPTIVE PROPERTIES OF THE VESTIBULO-OCULAR REFLEX

The brain shows a remarkable ability to adapt* the VOR to prevailing environmental circumstances. The VOR can compensate for the effects of disease and trauma and the changes that occur with growth and aging. From a profound loss of labyrinthine function on one or both sides to wearing a new spectacle prescription, the VOR must detect errors in performance and correct for them. Mechanisms exist to maintain balanced levels of tonic activity—to prevent spontaneous nystagmus—and to ensure calibrated compensatory responses to head motion, so that slow phases are of the correct amplitude, direction, and timing (phase). Other mechanisms and strategies also help stabilize the line of sight during head movement; they become especially evident when there is a loss of the peripheral vestibular signal. In this section we will discuss habituation, the short-term adaptation that produces the reversal phases of nystagmus, calibration of the VOR in response to imposed visual-vestibular mismatches, and then recovery from loss of labyrinthine function.

Vestibulo-Ocular Reflex Habituation

Although impaired vision during head movements is the basis for many adaptive changes in the performance of the VOR, the VOR shows

* We will not make a rigid distinction here between the terms "adaptation" and "compensation." Usually, "adaptation" is used in a more restricted sense, to imply adjustment in the basic vestibulo-ocular reflex, whereas "compensation" is used in a larger sense, to include the entire repertoire of ways, including substitution, prediction, and other cognitive strategies, by which patients recover from, and learn to live with, vestibular disorders. Habituation (see below) is the phenomenon in which there is a gradual diminution in the response to repetitions of an identical stimulus.

habituation (i.e., a reduction of time constant and gain) to repetitive stimuli in complete darkness. Habituation is most evident after repeated constant-velocity rotations or low-frequency continuous oscillations (stimuli outside the frequency range of most natural head rotations).[4,59,178] Analogous to other sensory systems, it may contribute to eliminating the persistent spontaneous nystagmus that follows a unilateral labyrinthine lesion. The vestibulocerebellum is involved in habituation as removal of the nodulus prevents it.[190] Functional imaging shows widespread changes in activation or deactivation in cerebral cortex and subcortical structures during habituation, which may relate to changes in the nystagmus pattern.[608] The relevance of habituation to clinical testing is that patients previously subjected to repetitive stimuli that contain a low-frequency component (for example, ice skaters who do long, high-speed spins), may have unusually low time constants of the r-VOR.

Short-Term Vestibulo-Ocular Reflex Adaptation that Produces Reversal Phases of Nystagmus

Adaptive mechanisms are also engaged by the presence of a persistent, unchanging vestibular stimulus. Such a stimulus almost never occurs in natural circumstances except when there is a lesion that creates an imbalance in vestibular tone between the two sides. This results in a spontaneous nystagmus. For example, with a constant-velocity rotation, after the original nystagmus dies out, a reversal phase of nystagmus may develop with slow phases in the opposite direction (i.e., the same direction as head rotation) (see Fig 1–6). This phenomenon probably reflects an adaptive mechanism, residing in both the brain stem and the peripheral vestibular apparatus, which has been activated by a persistent vestibular stimulus.[309,500] It has a time constant of action of about 80 seconds, so that its effect is completed in minutes. One natural cause of such a persisting vestibular signal is an imbalance in the tonic levels of activity due to a peripheral labyrinthine disturbance; the adaptation mechanism could help to nullify the pathologic spontaneous nystagmus. Such a mechanism, however, probably works best only for small degrees of imbalance; after a unilateral loss of labyrinthine function, it may take days for vestibular tone to be brought back into balance, eliminating the spontaneous nystagmus. Prolonged optokinetic stimulation also may cause ocular motor and perceptual aftereffects that are manifestations of motion habituation.[124] Like per-rotatory or post-rotatory nystagmus, optokinetic after-nystagmus may be followed by a reversal phase (OKAN II).

The adaptation mechanism producing the reversal phases of nystagmus is particularly prominent in infants.[873] Its action may become particularly obvious in patients with cerebellar lesions; it is responsible for the change in the direction of the slow phase that characterizes periodic alternating nystagmus (see Video Display: Periodic Alternating Nystagmus).[500] The reversal phase of head-shaking–induced nystagmus is another manifestation of this same mechanism.[364]

Visually Induced Adaptation of the Vestibulo-Ocular Reflex

The VOR functions in an inherently "open-loop" manner. Because of the brief periods and short latencies within which it must operate, immediate visual inputs cannot correct for most imperfections, because of the time taken in retinal processing. Consequently, the brain must continuously monitor the effectiveness of its VOR and adjust it accordingly when it malfunctions. Longer-term adaptive capabilities, based upon visual error signals during head motion, must be used.

ADAPTATION TO REVERSING PRISMS AND SPECTACLE LENSES

A dramatic example of the effects of changed visual demands upon the VOR are the consequences of viewing the world through head-fixed optical devices such as mirrors or prisms that laterally invert the world, left to right.[335,336,551] While wearing such devices, head turns cause the environment to appear to move in the same direction as head turning. After just a few minutes of head rotation during reversed vision, the gain of the r-VOR (measured during rotation in darkness) declines. Subjects also adopt strategies such as altering the pattern of head motion or using saccades to help stabilize gaze in this altered visual environment.[86,553] After removal of the optical device, gain rapidly returns to its previous value. With longer periods of exposure to visual inversion, changes in the VOR are retained for a longer period, such as overnight. In subjects who wear reversing prisms for 3 to 4 weeks, large changes of gain and phase occur that actually reverse their VOR; head rotations cause eye movements in the same direction. Thus, the gain and phase of the r-VOR are changed so that images are once again stable upon the retina during head movements. While these adaptive changes are taking place, subjects report symptoms of motion sickness, reflecting the conflict between vestibular and visual cues.[554]

A less extreme and more common visual demand on the VOR is wearing a spectacle correction. Spectacle lenses have a prismatic effect that is called rotational magnification, to distinguish it from the linear magnification that produces clearly focused images. This means, for example, that individuals who wear high-positive lenses (e.g., for aphakic correction or hyperopia) must rotate their eyes more when they attempt to change their line of sight, compared to when they are not wearing their glasses. Similarly, they will be required to rotate their eyes proportionally more during rotations and translations of the head in order to hold images steady upon the retina, compared to when they are not wearing glasses. Nearsighted (myopic) individuals who habitually wear negative spectacle lenses have lower values for the gain of the r-VOR than farsighted (hyperopic) individuals, or patients who have had their lenses removed and habitually wear positive spectacle lenses.[162] Individuals who habitually wear contact lenses show no such changes in the gain of the r-VOR; because the contact lenses rotate with the subject's eyes, there is no rotational magnification effect. Adaptation of the r-VOR to spectacle correction occurs rapidly in normal subjects. More than 50% of subjects show significant changes in the gain of the r-VOR after wearing telescope lenses for 15 minutes.[245] Older subjects are capable of developing such short-term adaptation, but the response is diminished.[631] Theoretically, habitually wearing a spectacle correction should lead to changes in the t-VOR but this has not been examined experimentally.

Changes in the gain of the r-VOR occur over a broad frequency range and not just at the testing frequency. With prolonged training at one frequency of rotation, however, adaptive gain changes are greatest at the training frequency.[512] If subjects wear '2X' magnifying lenses for several days during natural behavior, then an increase of the gain of the r-VOR is most evident for testing frequencies of rotation of the head greater than 2 cycles/second.[429] With shorter periods of wearing the lenses, however, adaptation may be greater for lower frequencies.[636] Amplitude nonlinearities, with less adaptation at higher velocities, may become apparent.[636] There are also differences in adaptive capabilities that can be frequency (high or low) or direction (up or down) dependent.[408,533] Critical to understanding why there are such differences in adaptive responses is consideration of an important principle of VOR, and presumably many other types of motor adaptation: the adaptive response is tailored to the context of the adaptive stimulus. Differences in how subjects move their heads under natural circumstances may influence the adapted response.

In addition to using optical devices, VOR adaptation can be studied by prolonged rotation of subjects while artificially manipulating the visual surround, either across the visual field,[479] or even in depth.[5] One can use an optokinetic drum that surrounds the subject, and rotate it in phase—in the same direction as chair rotation—to produce a decrease in the gain of the VOR, or out of phase—opposite the direction of chair rotation—to produce an increase in the gain of the VOR. If the amplitude of drum rotation is exactly equal to that of the chair, the required VOR gain would be 0.0 for in-phase viewing (so-called × 0 viewing) and 2.0 for out-of-phase viewing (so-called × 2 viewing). The usual duration for VOR training in these types of paradigms is an hour or two, although adaptation of the VOR can probably be detected within minutes of the onset of the change in the relationship between the visual and vestibular stimuli.[195] These relatively short-term adaptation experiments probably test only one type of vestibular adaptation, because the learned response is not sustained in the absence of continued stimulation. There is also a long-term adaptive process, taking days to weeks, rather than just minutes to hours, which gradually supervenes and leads to a

more enduring, resilient adaptive change.[401,406,407,458a,485] Thus, one must be cautious when extrapolating results from these short-term experiments to the long-term problems of patients adapting to chronic vestibular deficits.

Adaptive capabilities have been investigated in elderly subjects[631] and at higher frequencies (above about 0.75 Hz); their ability to increase the gain of the r-VOR adaptively is significantly diminished. Because the r-VOR is most needed to compensate for the high-frequency components of head rotation, a loss of adaptive capability in elderly patients could account for their more disabling and persistent symptoms after a vestibular loss. Furthermore, with aging, patients with deficient vestibular responses lose some ability to substitute corrective saccades for hypometric slow phases.[804,805]

CROSS-AXIS ADAPTATION OF THE VESTIBULO-OCULAR REFLEX

A variety of paradigms have been used to demonstrate the wide repertoire of VOR adaptive responses, including the ability to change the direction, phase (timing), and amplitude of the VOR. For example, if the head is rotated horizontally (in yaw) while the visual display is synchronously rotated vertically, after a training period, horizontal rotations in darkness will produce eye movements that have a vertical component.[24,298,465,651,727,851] Similar adaptation occurs with head rotation in pitch and horizontal pursuit eye tracking,[300] or head rotation in yaw and torsional optokinetic stimulation.[816] This *cross-axis plasticity* accords with electrophysiological evidence that secondary neurons in the vestibular nucleus receive inputs from one, two, or all three pairs of semicircular canals.[52] Furthermore, during cross-axis training, neurons in the vestibular nuclei that are normally maximally sensitive to pitch axis (vertical) stimulation increase their sensitivity to yaw axis (horizontal) rotation,[678] providing a neurophysiologic substrate for the change in direction of the VOR. Similar considerations apply to the fact that wearing left-right reversing prisms calls for a change in the torsional (roll) but not vertical (pitch) VOR gain. Such a selective change in the VOR takes place even though both torsional and vertical signals are carried on the same vestibular afferents.[78,90,91]

A matrix analysis of the problem of producing slow phases in a direction orthogonal to head motion, or producing a change in torsional gain alone has been presented by D.A. Robinson.[703,703] Thus, one matrix represents the vectors of the semicircular canals, a second matrix represents the pulling actions of the extraocular muscles, and a third matrix represents the strength of central connections between vestibular neurons and ocular motoneurons. The third matrix—the brain stem matrix—makes the necessary adjustments both for the contributions of the different semicircular canals to the detection of the axis of head rotation and for the different pulling directions of the extraocular muscles that are innervated by the primary VOR reflex pathways. When head movements are artificially dissociated from apparent motion of the visual environment, as described above, then a change in the central, brain stem matrix must occur so that, for example, vertical eye rotations are coupled to horizontal head rotations, or the torsional VOR gain is selectively enhanced or depressed. A similar matrix analysis has been developed for binocular responses to the VOR.[839]

OTHER FORMS OF VESTIBULO-OCULAR REFLEX ADAPTATION

Other examples of VOR adaptive capabilities include changes in dynamic characteristics such as the phase (timing) of the VOR.[391,480,481,667,695,696] Adaptation of the phase of the VOR also leads to a change in the time constant of the ocular motor velocity-to-position integrator (either making it less reliable ('leaky') or unstable), emphasizing the important role of the neural gaze-holding integrator in assuring that compensatory slow phases have the correct phase relationships during motion of the head.[171,391,481,758] Disconjugate adaptation of the r-VOR may occur in response to a unilateral muscle palsy,[837,880,881] for example, or to wearing prisms in front of one eye.[627] Such a capability is especially important for a correct compensation to the translational component of head (orbit) motion, because the eyes must rotate by different amounts whenever the point of regard is near to the subject. The vertical and torsional VOR undergo similar adaptive adjustments as does the horizontal VOR though in the case of torsion the mechanisms may be somewhat different.[90,91,771,816]

Otolith-ocular reflexes are also subject to adaptive control. VOR learning acquired with training during upright (yaw axis) rotation is transferred to the otolith-derived modulation component of OVAR.[477,857] Similarly, there is (inappropriate) transfer to otolith-mediated slow-phase compensation during orthogonally directed rotations (head-over-heels).[664] Prolonged centrifugation can lead to changes in the roll (torsional) r-VOR,[356] though 2 hours of static lateral head tilt (up to 34°) in monkeys induced no change in ocular counterrolling.[782] The response of the VOR to translation of the head is also under adaptive control.[391,476,682,737,857,869,909] In the absence of canal-driven responses, otolith-ocular responses to a changing gravity vector (which can occur when rotation is around an axis tilted away from the vertical) are potentiated, leading to improved stabilization of gaze during off-axis rotation of the head.[30]

Cognitive Control of Vestibulo-Ocular Reflex Adaptation

Although a visual stimulus (motion of images on the retina) is the main determinant of the pattern of these adaptive changes of the VOR, even imagination of a visual stimulus can be enough to bring about plastic changes in the gain of the r-VOR, although at about half the rate that occurs when visual stimuli are used.[552] Indeed, simply imagining body rotation can lead to compensatory slow-phase eye movements.[704] Along these lines,[266] it has been shown that just paying attention to, without even looking at, the new location of a target after a head rotation (i.e., using a position rather than a retinal image motion error), leads to adaptive modification of the VOR. Thus, what are usually called psychological factors—motivation, attention, effort, and interest—may actually play a more specific role in promoting adaptive recovery. Even an afterimage placed on the retina or strobe illumination, neither of which allow for retinal image motion, can stimulate adaptation of the r-VOR.[300,529,749] There are perceptual concomitants of adaptation of the VOR that accord nicely with the ocular motor responses that are measured in darkness.[102]

Context-Specific Vestibulo-Ocular Adaptation

Probably one of the more critical aspects of successful vestibular compensation in natural circumstances is a capability for VOR adaptive responses to be expressed on the basis of context. The attitude of the head relative to gravity, the position of the eye in the orbit including the vergence angle, and the frequency content and pattern of the head movement are potent contextual cues for the gating of different vestibular responses.[480,505,668,748,753,809,866,886,888,889] For example, the horizontal r-VOR can be made to have an increased gain when the vertical eye position is up in the orbit, and a decreased gain when the eye is down in the orbit,[751] or the horizontal r-VOR can be adapted selectively for different viewing distances.[505] In other words, the brain has mechanisms to enlist different learned vestibular responses depending upon the circumstances in which they must occur. This type of adaptive capability has important clinical implications for the programs of physical therapy that are prescribed for patients with vestibular deficits. The specific exercises should be close to the type of stimuli that are encountered naturally and produce symptoms if the VOR is not working correctly.

Mechanisms of Recovery from Lesions in the Labyrinth

Thus far, we have discussed adaptive responses that affect the gain of the VOR symmetrically. But a common and important clinical problem is how the brain compensates for unilateral labyrinthine lesions (see Box 11–1, Chapter 11). What factors influence the rate and pattern of recovery from a peripheral vestibular lesion?[222,223,230,612,762,763] Here we will highlight some key features based upon a study of experimental, unilateral labyrinthectomy in monkeys, which illustrates how different parts of the recovery process depend upon visual or non-visual factors.[286,897] In the first 24 hours following labyrinthectomy in the monkey, there is a head tilt and turn towards the side of the lesion. With the head stationary, spontaneous nystagmus, with slow phases directed towards the side of the lesion, is present in

light and darkness. The nystagmus indicates a static vestibular imbalance. The slow-phase velocity in the dark (20 degrees per second to 60 degrees per second) is much greater than in the light (up to 4 degrees per second), illustrating that visual fixation suppresses this nystagmus. The velocity of the slow phases of nystagmus declines during the next few days, irrespective of whether the monkeys are kept in a dark or an illuminated environment. Moreover, in monkeys that have previously undergone bilateral occipital lobectomy, resolution of spontaneous nystagmus occurs at a similar rate. Thus, recovery from the static imbalance that follows a unilateral labyrinthine lesion does not depend upon vision. Recovery of static balance from unilateral labyrinthine loss in humans may never be complete; in darkness, some patients show spontaneous nystagmus years after their lesion. The basis of the resolution of the spontaneous nystagmus after a unilateral loss of function is largely a restoration of activity on the side of the lesion.[762]

Other factors may supervene early in the compensation process, including, for example, suppression of activity on the intact side.[538,699] Later during compensation, subjects may employ strategies apart from changing the gain of the slow-phase response, especially the use of saccades to substitute for hypometric slow phases.[87,96,652,653,732,771a,801] An additional finding after recovery from labyrinthectomy in monkeys is an increased response to cold caloric stimulation of the normal ear. Similar findings have been reported in humans.[422] The change in caloric responses may represent an adaptive increase in vestibular nucleus sensitivity on the intact side.

Recovery from the dynamic vestibular imbalance that follows unilateral labyrinthectomy depends on *visual inputs*; the gain of the VOR does not increase in monkeys kept in darkness. Moreover, monkeys that have undergone bilateral occipital lobectomy before labyrinthectomy show only a partial recovery, with little compensation for high-velocity stimuli. This finding suggests that both striate and extrastriate visual pathways play a role in the recovery of dynamic vestibular responses following unilateral labyrinthectomy. These findings contrast with the recovery from static vestibular imbalance, which does not depend upon visual factors.

Presumably, the contribution of the occipital lobes is that they transmit information about slippage of images on the retina during head movements to the more caudal structures that, in turn, use this error information to readjust the dynamic performance of the VOR. The nucleus of the optic tract (NOT) in the pretectal region of the midbrain is one such structure shown to be important in VOR adaptation. The NOT receives visual information from the cerebral cortex as well as directly from the retina. It has a strong projection to the inferior olive and to other brainstem nuclei that also project to the cerebellum. Lesions in the NOT interfere with compensation to unilateral labyrinthectomy,[773] and VOR adaptation in general.[887] But the NOT does more than simply relay visual information for adaptive changes in the VOR since lesions in the NOT also lead to change in the baseline VOR gain. Whether or not the NOT is important for maintaining long-term adaptive changes is not known but presumably that is the case. The NOT may be the anatomical substrate by which a patient with cortical blindness and monkeys following bilateral occipital lobectomy still showed at least some VOR adaptive capability.[286,625] The cerebellum must be constantly appraised of the need for adaptive recalibration and visual inputs are critical. Even if a patient can "see" in the usual sense, if lesions in the brainstem interfere with the transmission of visual information to the cerebellum, the VOR can still become uncalibrated.[320] The role of the NOT in smooth pursuit is discussed further in Chapter 4.

Recent studies have shown that recovery following unilateral labyrinthine lesions is less complete when stimuli are comprised of high accelerations or high frequencies because of Ewald's second law.[223] Certainly some adaptation does take place, requiring a recalibration of peripheral activity coming from the intact labyrinth. This process may use information from irregular afferents that are part of a phasic (and possibly nonlinear) pathway, which runs in parallel with a tonic, linear pathway to mediate the VOR.[181,182,491,492,643]

Recovery from peripheral vestibular lesions depends in part upon the degree to which peripheral function is spared. Plugging of individual semicircular canals has shown that compensation can be partly restored by using information from the remaining intact canals though residual function in the plugged semicircular canal may be important, too.[885] The spatial tuning of information from the intact canal (as a function of the plane of rotation) is readjusted centrally so that it can provide a better signal of rotation in a plane close to that of the plugged canal.[22,108,112,398]

Vestibulo-ocular reflex adaptation and compensation depend upon the integrity of a number of structures, including the cerebellum and perhaps the vestibular commissure. After destruction of one labyrinth, vestibular nucleus neurons ipsilateral to the lesion are driven exclusively by the contralateral vestibular nucleus, through the vestibular commissure; this finding led to the suggestion that this structure is important in compensation from peripheral vestibular lesions.[341] A change of neural tone in the vestibular nucleus, however, independent of changes in commissural gain, could also be important.[169,273,284] Such a change of neural tone might be achieved by the deep cerebellar nuclei or by intrinsic factors within the vestibular nuclei. Changes in the membrane properties of vestibular neurons, and in intrinsic pacemaker activity also may be important in the recovery after unilateral labyrinthine loss.[82,83,229,341,360a,506,700] A number of biochemical changes accompany adaptation; whether they are primary or secondary is largely unknown.[38,167a,229,230,329,330,341,360a,415,469,471,472,506,521,526,714,760,761,764,905] Compensation for a bilateral loss of labyrinthine function includes a number of compensatory responses and strategies, which are further discussed below (Pathopysiology of Bilateral Loss of Vestibular Function).

VESTIBULOCEREBELLAR INFLUENCES ON THE VESTIBULO-OCULAR REFLEX

Anatomical Pathways by Which the Vestibulocerebellum Influences the Vestibulo-Ocular Reflex

The vestibulocerebellum consists of the flocculus, nodulus, ventral uvula, and ventral paraflocculus.[841,842] The flocculi and adjacent paraflocculi share anatomic connections and physiologic properties. The flocculus receives bilateral, mossy fiber inputs, primarily from the vestibular nuclei and nucleus prepositus hypoglossi (NPH), but also from the pontine nuclei and nucleus reticularis tegmenti pontis. The climbing fiber inputs to the flocculus are from the dorsal cap of the contralateral inferior olivary nucleus.[490,890] Another input to the flocculus is from the cell groups of the paramedian tracts (PMT), which may relay an efference copy of eye movement.[161] Thus, the flocculus receives vestibular, visual, and ocular motor signals. In primates, the flocculus probably receives relatively few direct vestibular nerve afferents, though the nodulus is more richly innervated directly from the vestibular nerve.[70,490,604] The flocculus projects to the ipsilateral vestibular nuclei, y-group, and the basal interstitial nucleus of the cerebellum.[489] Particularly important are the floccular target neurons (FTN) in the vestibular nuclei, which probably play a role in vestibular adaptation.[96a,97,402] These anatomical connections are summarized in Box 6–10, in Chapter 6.

Electrophysiological Aspects of Vestibulocerebellum Control of the Vestibulo-Ocular Reflex

Recordings from the flocculus of alert, trained monkeys have revealed a particular group of Purkinje cells that do not modulate their discharge during vestibular eye movements in darkness, nor during head rotation while fixating a stationary target. Their discharge modulates in relation to *gaze velocity* (velocity of the eye in space) during pursuit of a moving target with the head still nor during combined eye-head tracking.[483] The role of these gaze-velocity Purkinje cells in the control of eye movements is not settled; they may play a role both in the on-line modulation of the VOR using visual-following reflexes, and in the long-term changes in the VOR related to adaptation partly via the y-group (see Box 6–8).[96a,98,118,152,190,401,402,432,482,513,514,606,647,686,884] The flocculus also plays a role in recovery of function after unilateral labyrinthine loss. Although restoration of relatively small degrees of imbalance between the vestibular nuclei can probably take place independently of the flocculus,[361] large amounts of spontaneous nystagmus and the recovery of amplitude and symmetry of gain during head movement probably require the flocculus.[50,470,473,594] The Purkinje cells in the flocculus may also participate in adjusting the gain of the r-VOR or the

t-VOR, when subjects view targets that are close to the head.[766] Another role for the flocculus may be in modulating the cervico-ocular reflex, especially in suppressing the reflex when it would lead to image motion on the retina.[321] The flocculus appears to have a more prominent role in adjusting the passive, gaze-stabilizing VOR rather than in adjusting the VOR during active combined eye-head changes of gaze.[79] Still unknown is what role the vestibulocerebellum plays in the control of the VOR in response to linear accelerations, both static counterrolling and the t-VOR.

Patients with cerebellar disorders may show deficits in the t-VOR but whether this arises from involvement of the vestibulo-cerebellum or other parts of the cerebellum including the dorsal vermis is unknown. Patients with cerebellar deficits also show a disorder of eye alignment—skew deviation that changes sense with right and left lateral gaze—which has been interpreted as a manifestation of disturbed processing of otolith information for static head tilt in pitch similar to the ocular tilt reaction (OTR) for static head tilt in roll.[894] It is possible that that the nodulus, which is important for orienting the vector of the slow phase of nystagmus relative to gravity during low-frequency angular VOR responses, also contributes to low-frequency linear VOR responses such as head tilt. Thus eye alignment with head tilt might become abnormal with nodulus lesions. Clearly our knowledge of the role of the cerebellum in the control of static and dynamic responses to linear acceleration is meager and demands further investigation both in experimental models and human patients with cerebellar disturbances.

Effects of Vestibulocerebellar Lesions on the Vestibulo-Ocular Reflex

Experimental lesions of the primate flocculus and parafloccculus produce relatively small changes in rotational vestibular responses; the gain of the r-VOR may be slightly higher or lower.[190,845,903] On the other hand, the ability to adapt the gain of the r-VOR in response to visual demands is abolished.[513,727] Human patients with cerebellar disease may show abnormalities in adaptation of the r-VOR;[301, 710,883] these deficits are likely due to involvement of the flocculus. Optokinetic nystagmus and the velocity-storage mechanism are relatively preserved after flocculectomy, but smooth tracking, either with the head still or moving, is impaired.[845,903] The output of the gaze-holding integrator—the step of innervation—cannot be maintained when the eye is put into an eccentric position, producing gaze-evoked nystagmus. The step is also not matched correctly to the amplitude of the velocity command that moved the eye to its new position, producing postsaccadic drift (glissades). Little is known about the effects of vestibulocerebellar lesions on the t-VOR. Since pursuit is impaired, however, and there is a close functional symbiosis between pursuit and the t-VOR, one might expect severe deficits in the t-VOR with vestibulocerebellar lesions, but this remains to be shown. The known deficits with vestibulocerebellar lesions are summarized in Box 12–2.

Experimental lesions of the nodulus and ventral uvula of monkeys (Box 12–3, Chapter 12) maximize horizontal velocity storage, which increases the time constant of the horizontal VOR. The lesion also prevents habituation of the VOR, impairs tilt-suppression of post-rotatory nystagmus, disturbs the reorientation of the velocity-storage mechanism to earth-horizontal with head tilt, alters vertical OKAN, and causes periodic alternating nystagmus in darkness.[404,846,862,865] In monkeys, but presumably not in humans (who show little torsional velocity storage),[735,735,736] ablation of the nodulus and ventral uvula decreases the time constant of the roll (torsional) VOR.[17]

Role of Cerebellum in Vestibulo-Ocular Reflex Adaptation

The exact sites and specific mechanisms underlying the cerebellar contribution to learning in the VOR are still uncertain.[7,50,98,99, 118,152,167a,382,432,458a,485,545,606,686] Ito proposed that the error signal for an inadequate VOR—drift of images on the retina—is relayed, via the inferior olivary nucleus and climbing fibers, to Purkinje cells in the flocculus.[430,432] Based upon this visual information, and vestibular inputs relayed by mossy fibers and then onto the parallel fibers of granule cells, Purkinje cells would be able to make appropriate changes in the VOR via their projections to

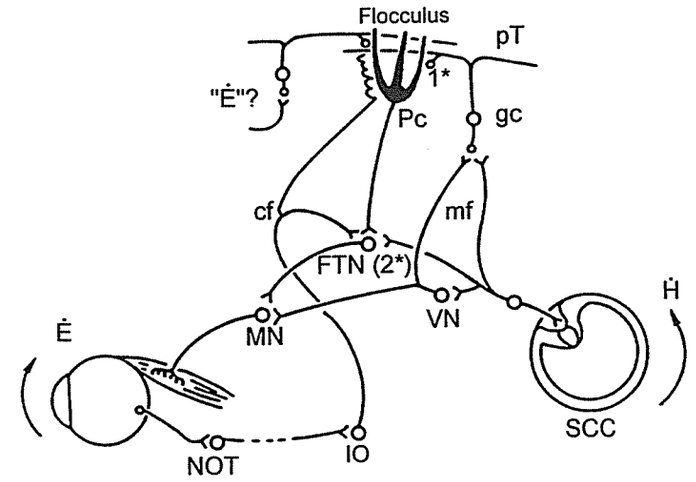

Figure 2–10. Hypothetical scheme to account for vestibulo-ocular adaptation. Head velocity (Ḣ) is transduced by the semicircular canals (SCC) and sent to the vestibular nuclei (VN) to be relayed, via a three neuron arc, to the motoneurons (MN), to create an equal but opposite eye velocity (Ė). The canal signal is relayed to the flocculus (Floc) on mossy fibers (mf) that are axon collaterals of either first- or second-order vestibular neurons, via granule cells (gc) and their parallel-T fibers to Purkinje cells (Pc). Retinal image motion is sensed by direction-selective cells in the retina, relayed through the nucleus of the optic tract (NOT), to the inferior olivary nucleus (IO), and thence to the Pcs on climbing fibers (cf). The Pc project to a subset of second- or third-order cells in the VN called floccular target neurons (FTN), which also receive an axon collateral from the cfs. The Pc's are also thought to receive a copy of the eye velocity signal (Ė). According to Ito, the error signal is carried by cfs, and the modifiable synapses are on Pc dendrites at site 1*. According to Lisberger and colleagues, the Pc carry the error signal and the main modifiable synapses are on FTNs at site 2*. (From Luebke and Robinson,[522] with kind permission of Springer Science and Business Media.)

the vestibular nucleus (Fig. 2–10). Thus, it was proposed that the vestibulocerebellum is the site of a form of motor learning, due to modifiable synapses between parallel fibers and Purkinje cells. Ito has proposed that this learning is due to a long-term depression (LTD) of synaptic transmission from parallel fibers to the Purkinje cell.[431,432] This synaptic change depends upon calcium ions and glutamate receptors, and is induced by the nearly simultaneous arrival of signals from climbing fibers and parallel fibers on Purkinje cells.

Although Ito's flocculus hypothesis has many attractive features, it does not account for all the experimental data in primates, including the behavior of the so-called gaze-velocity Purkinje cells previously discussed.[511,578,696] The "flocculus hypothesis" does not completely account for the effects on VOR adaptation of silencing the climbing fibers of the inferior olivary nucleus with a local anesthetic, or experimentally stimulating climbing fibers to produce "floccular shutdown."[246,522] Furthermore, a critical issue in VOR learning is how the correct relative timing between the arrival of signals conveying information about motion of the head, and motion of images on the retina (the error signal), is deciphered by floccular Purkinje cells.[511,696] Likewise there is evidence for differential regulation of the gain of the VOR and its dynamic properties. Low-frequency training stimuli tend to produce frequency-specific changes in gain; high-frequency training stimuli tend to produce changes in gain that are relatively frequency-independent.[695] It has been suggested that the frequency-specific changes are mediated by calcium channels, and the frequency-independent changes by calcium-activated potassium channels.[264] One source of the discrepancy between Ito's work and the results described in primates may be disagreement about what the flocculus is. Parts of what has traditionally been called the flocculus are probably part of the ventral paraflocculus, which may be more associated with pursuit rather than with VOR adaptation.[431,603,605,606,686,842]

An alternative explanation is that the flocculus, rather than being the sole site of VOR learning, serves other functions in VOR adap-

tation.[99,118,152,510,511,606,648] It could provide an error correction signal to the neurons in the vestibular nucleus, called the flocculus target neurons (FTN), which would be one site of motor learning for VOR adaptation (Figure 2–10). Perhaps adaptive changes in the amplitude of the VOR would be mediated by this mechanism. The flocculus, however, could still be a site of learning for other types of vestibular adaptation (e.g., the response to low-frequency training stimuli, the responses that require a change in the timing or dynamic response of the VOR, or in context-driven VOR learning). The cerebellar flocculus, with its rich sources of afferent information and internal copies of motor commands, would be ideally poised to gate different VOR responses based upon the circumstances in which they are needed.

As discussed above the flocculus plays a role in recovery of function after unilateral labyrinthine loss. The inferior olive, which presumably relays critical error signals to the flocculus, shows unilateral changes in mRNA expression of brain-derived neurotrophic factor following unilateral loss of labyrinthine function.[508]

Of course, a number of other adaptive strategies are used to compensate for a vestibular loss, apart from adjusting the gain of slow phase of the VOR. They include preprogramming of compensatory eye movements.[458] Whether or not the cerebellum is involved in these "higher level" strategies is not known. It has been shown, however, that when a rabbit is exposed to sustained sinusoidal oscillation of the head, some climbing fibers in the nodulus of the rabbit discharge in a sinusoidal fashion after the animal stops rotating.[71] This finding is compatible with the idea that the cerebellum can learn patterns of vestibular stimulation and generate them even after the actual stimulus has ceased.

As discussed above, many neurotransmitters and neuropeptides have been implicated in the process of vestibular adaptation. In the vestibulocerebellum, nitric oxide, NMDA receptors, acetylcholine, and catecholamines appear to be important.[230] Long-term depression (LTD) has been implicated in the cerebellar contribution to VOR adaptation and long-term potentiation (LTP) may also be important.[275,342,432,485,830] Specific transmitters may relate to the direction (increase versus decrease) or the frequency spectra (high versus low) of a particular adaptive response,[167a,458a,507,673] which, at least hypothetically, may relate to the behavioral differences in adaptation related to frequency content or direction of response (e.g., up versus down in direction, or increase versus decrease in amplitude).[408,673]

Numerous computational models have been proposed to account for many aspects of VOR learning including adaptation of the phase and gain of the VOR, and restoration of dynamic balance after unilateral lesions. Many such models include a potential role for the cerebellum.[98,118,315,343,407,432,511,663,677,696,786,871,892] But often lacking from these models are correlations between behavior and neural activity.

VESTIBULAR SENSATION AND THE ROLE OF THE CEREBRAL HEMISPHERES IN THE VESTIBULO-OCULAR REFLEX

Inputs from the labyrinth constitute the basis for a "sixth sense".[128] Thus, rotation in the dark at a constant velocity produces a sensation of turning that declines, as do the induced eye movements. Similarly, one can detect and identify static tilts of the head and body. Vestibular sensations are usually accompanied by congruent visual and somatosensory inputs; when conflict arises, discomfort and motion sickness can result.[100,114] During natural activities, it is necessary to distinguish between sensations due to self-motion and those due to movement of objects in the environment. One insight into how this is achieved is the observation that real or perceived thresholds for detecting motion of objects in the environment are elevated during locomotion.[674] Such a change in perceptual thresholds may contribute to the ability to maintain a sense of a stable world during locomotion, and act as an adaptive strategy in patients with vestibular loss and oscillopsia.[95,142,151,349,452,570,610,745]

The vestibular system also plays an important role in the perception of the position of the head on the body, the body in space, and how sensory conflicts might be resolved.[457,487,567,568] Evaluation of perception, including the sense of where the head is pointing in darkness, and the attitude of the visual or body vertical may be valuable in detecting lesions in various parts of the vestibular system, from the labyrinth to the cerebral cortex.[95,128,296,426,427,452,610,729,828]

A number of cerebral cortical areas receive vestibular inputs and/or project to the vestibular nuclei.[88,115,116,296,360,498,796] Much has been learned from functional brain imaging and cortical stimulation, which have supplemented the more traditional studies that use anatomical techniques, single-unit recordings from awake behaving animals, and clinical studies of the effects of lesions or seizures.[80,81,133,238,256,262,268a,269,390,449,474,475,515,608,722a]

The vestibular nuclei project diffusely to the lateral and inferior portion of the ventroposterior lateral thalamic nucleus (VPL), where activity related to head rotation in darkness can be recorded.[157] Thalamic neurons appear to receive their major inputs from excitatory rather than inhibitory secondary vestibular neurons, though the inhibitory neurons are clearly important for the VOR itself.[534] Stimulation of the human thalamus during operations for intractable pain or movement disorders can produce sensations of movement[389] and lesions there can produce changes in cerebral cortex activation, as reflected in functional imaging, during vestibular stimulation.[255] In monkeys, projections from the VPL pass rostrally to parietal, parieto-insular, and frontal cortex.[6] These several regions of vestibular cortex include area 2v at the anterior tip of the intraparietal sulcus, area 3av in the lateral sulcus, the medial superior temporal visual area (MST), and the parieto-insular-vestibular cortex (PIVC) deep in the Sylvian sulcus posterior to the insular cortex. In this last area, most of the cells are multi-modal, often responding to labyrinthine, visual (optokinetic), proprioceptive (usually from the neck), or somatosensory inputs from the skin. Neurons can be excited for ipsilateral (type I) or contralateral (type II) rotation, as is the case for neurons in the vestibular nuclei. Optokinetic and labyrinthine inputs can be synergistic (excited for opposite directions, as occurs during natural head rotation) or antagonistic (excited for the same direction). Neurons that carry inputs from the neck and labyrinth also may be synergistic or antagonistic. The three aforementioned cortical vestibular areas—2v, 3a, PIVC—are strongly interconnected with each other and with the opposite hemisphere. Area PIVC, in particular, seems to be a nexus for spatial orientation, as it also receives projections from areas 3aH (hand), 6pa, 7a,b, 8a, cingulate gyrus, and the visual temporal Sylvian area. Recent studies have defined further the roles of VIP (the ventral-intraparietal area) and periarcuate cortex in the frontal lobes in this cortical vestibular circuit.[138,139,717,718,779]

The vestibular projections to the cerebral cortex presumably carry information for spatial orientation, but they could also be involved in other aspects of vestibulo-ocular control, including carrying information for cerebral influences on vestibular adaptation, and in gating different vestibular responses, related to context or anticipation of an upcoming required motor response.[487,832] Indeed there are strong descending projections to the vestibular nuclei—both ipsilateral and contralateral—that could mediate these effects,[296,360] and there are widespread descending projections from the cerebral cortex to the vestibulocerebellum that could be important in higher-level modulation of the VOR.

In humans, multiple cortical areas receive vestibular signals.[80,131,133,238,256,262,269,274,449,474,475,515,589,608,781] Functional imaging has shown that optokinetic stimuli activate many of these same areas, again emphasizing the symbiosis between vision and labyrinthine stimulation in the processing of information about motion and spatial orientation.[248,249,258,453,478] Vection—the illusory sense of motion induced by purely visual stimuli—is likely mediated by these same areas though there may be some segregation between areas that mediate sensations of rotation and of translation.[249] The temporal lobes have been thought to mediate a vestibular sense, based on Penfield's observation that stimulation of the superior temporal gyrus of awake patients caused sensations of bodily displacement.[650] He and others also reported focal seizures—vestibular or "tornado" epilepsy—starting in this area, with auras consisting of sensations of rotation. Similar seizures, sometimes with epileptic nystagmus (see Video Display: Disorders of Gaze Holding), and even skew deviation, have subsequently been reported in association with focal discharges in frontal, parietal, or temporal lobes.[308,316,454,774] PET and fMRI studies have identified cortical areas responding to caloric stimulation in humans. The results largely agree with the anatomic and physiolog-

ical studies described above (see Fig. 6–8).[116,117,294,840] Ice water produces predominantly contralateral activation. In addition to the "vestibular" cortical areas described above, the anterior cingulate cortex, insula, and putamen are activated during caloric stimulation. Patients with vestibular neuritis show a similar pattern of activation,[80,269] though patients with more central vestibular nucleus lesions, such as Wallenberg's syndrome show different patterns.[257] Humans with lesions in cerebral cortex (probably in a region homologous to PIVC and nearby parietal cortex) show altered perceptions of the subjective visual vertical.[128,128,390,711a] and disturbances of circularvection.[392,775] They may occasionally have rotational vertigo.[113,135,240] Lesions in PIVC also produce deficits in generating memory-guided saccades to a previously seen target, after the head is displaced to a new position in the dark.[428] Sensations of linear motion can be induced artificially with electrical stimulation, and naturally during seizures, in the paramedian area of precuneus cortex.[878]

Several important principles have emerged from the many recent functional imaging studies of the vestibular system.[80,123,133,255,262] First, activation with unilateral vestibular stimulation is asymmetric, greater in the hemisphere ipsilateral to the stimulated ear. Second, there is an overall predominance in the non-dominant hemisphere, which is related to handedness. This finding agrees with greater asymmetries of vestibulo-ocular function in patients with right hemisphere lesions,[833] and the general importance of the non-dominant hemisphere in spatial orientation and attention and neglect. Thirdly, there is a directional dependence; the hemisphere ipsilateral to the fast phase of nystagmus is activated more strongly. Fourthly, vestibular stimulation not only leads to activation in some areas of cortex (e.g., parietal-insular vestibular cortex), but also relative deactivation in other areas of the cortex (e.g., bilateral occipital visual cortex). Visual stimulation alone leads to a reciprocal pattern with activation in occipital cortex and deactivation in parietal-insular cortex. These findings support the idea of a reciprocal visual-vestibular interaction used for spatial orientation and motion perception, and for resolving conflicts between incongruent sensory inputs. Finally, there is considerable 'cross-talk' between the two cerebral hemispheres, which could be used to resolve sensory conflicts (e.g., when one hemisphere 'sees' a moving visual world and the other 'sees' a stationary visual world) by adjusting the relative weights of the two conflicting sensory inputs depending upon the task at hand.

The large amount of new information about the contributions of the cerebral cortex to vestibular perception and to the control of the VOR itself indicates that the new approaches using functional imaging and other types of stimulation and recording techniques are rich and promising areas for clinical investigation.

CLINICAL EXAMINATION OF VESTIBULAR AND OPTOKINETIC FUNCTION

General Principles for Evaluating Vestibular Disorders

Here we apply the basic principles already discussed to the clinical and laboratory evaluation of the patient with vestibular disease (see Appendix A for a summary, and Video Displays: Disorders of the Vestibular System and Positional Nystagmus). A more systematic treatment of specific vestibular disorders is given in Chapter 11. The reader is referred to neurootologic texts for details on otoscopy, audiometry, and vestibulospinal testing.[58,420] We will begin by recapitulating certain important physiologic properties that will guide the examination.[163]

First, to maintain steady gaze during head rotation, the r-VOR produces eye movements that compensate for head rotations. VOR gain (eye velocity/head velocity) and phase (temporal relationship between input and output during sinusoidal stimuli) are used to quantify this reflex. Phase relationships during sinusoidal rotations, and measurements of the time course of decay of the response to constant-velocity stimuli (velocity steps), provide a measure of the time constant of the r-VOR. The time constant is a function of both peripheral vestibular properties and central velocity storage.

Second, when the head of a healthy subject is stationary, the left and right vestibular nerves and nuclei show resting discharge rates (vestibular tone) that are balanced. It is around this level of tone that compensatory slow

phases are generated in response to head motion, either rotations or translations. This is accomplished by a 'push-pull' system in which motion in one direction causes one side (the side ipsilateral to head motion) to be excited and the other side inhibited. If disease causes a static imbalance of vestibular tone, a spontaneous nystagmus results (see Box 10–1, in Chapter 10). This imbalance causes slow phases with horizontal components directed toward the side with lower tonic activity (quick phases away from the side of the lesion).

Third, disease can also lead to a dynamic imbalance during head rotation and translation. This is similar to the directional preponderance of caloric testing (discussed later) and causes, for example, an r-VOR gain greater for head turns away from the side of the lesion than for head turns toward it.

Fourth, vestibular deficits are more easily appreciated with high acceleration, high velocity, and high frequency stimuli because Ewald's second law (excitatory stimuli are more effective than inhibitory stimuli) is most evident when the vestibulo-ocular reflex must operate under conditions that exceed the range in which the normal 'push-pull' mechanism can operate effectively.

Static otolith-ocular reflexes are relatively vestigial in human beings but disturbances of otolith pathways cause characteristic symptoms and signs including disturbances of the subjective visual vertical, and skew deviation, ocular counterroll, and head tilt.[126,127,149,268,352,362,455,633] With acute unilateral vestibular loss, the translational VOR elicited by side-to-side stimulation and the rotational VOR elicited with head impulses, are both abnormal for ipsilaterally directed head motion.[617]

Both the optokinetic and smooth pursuit systems supplement the VOR during sustained rotations in the light so that compensatory eye movements can be maintained as vestibular input decays. To evaluate the optokinetic system alone, relatively independent of pursuit, it is necessary to study optokinetic after-nystagmus (OKAN) in darkness.

History-Taking in Patients with Vestibular Disorders

Patients with vestibular disease may complain of disequilibrium, unsteadiness, or vertigo, which often reflect imbalance of vestibular tone. Vertigo is a distressing, illusory sensation of motion (literally, turning) of self or of the environment.[142] As distinct from one's perception of self-motion during natural locomotion, vertigo is linked to impaired perception of a stationary environment. The mismatch between the actual sensory inputs and the expected pattern of sensory stimulation with the head stationary causes vertigo. The nature of the vertigo may distinguish between disturbances of the semicircular canals and the otoliths. Rotational vertigo connotes disturbance of the semicircular canals or their central projections, whereas sensations of body tilt or impulsion (e.g., lateropulsion, levitation, translation) imply a disturbance in the otolith system.

Patients with rotational vertigo due to acute, peripheral vestibular lesions are often uncertain of the direction of their vertiginous illusions. This is because their vestibular sense indicates self-rotation in one direction, but their eye movements (the slow phases of vestibular nystagmus) cause visual image movements that, when self-referred, connote self-rotation to the opposite side. It is worthwhile to evaluate the vestibular sense alone by asking specifically about the perceived direction of self-rotation with the eyes closed, thus eliminating possible confounding visual stimuli. On the other hand, with the eyes open, one should ask about the direction of image motion, from which one can deduce the direction of the nystagmus. The direction of the slow phase of nystagmus is usually reported to be opposite to the direction of apparent motion of the visual world.

Complaints of tilts of the perceived world or body are often encountered in patients who have suffered Wallenberg's Syndrome (Lateral Medullary Infarction). Such patients may describe, for example, a 180-degree rotation of the environment, so that they see the floor where the ceiling should be; these complaints should not be dismissed as fanciful. Again, one should also eliminate conflicting visual stimuli by asking about the perception of the body when the eyes are closed.

Oscillopsia is an illusory, side-to-side or up-and-down movement of the seen environment. When brought on or accentuated by head movement, it is usually of vestibular origin and reflects an inappropriate VOR gain, direction

or phase. Vision becomes blurred so that, for example, fine print on grocery items can only be detected if the patient stands still in the store aisle. In the most severe cases, even the transmitted pulsations of the heart may interfere with vision.[437]

The Clinical Examination of Patients with Vestibular Disorders

Our strategy will be (1) to determine if any static or dynamic vestibular imbalance is present; (2) to determine if a change in head position or other maneuvers will induce an imbalance; (3) to estimate the gain and direction of the VOR. In certain circumstances we will elicit vestibular nystagmus by rotating the patient, and perform bedside caloric testing. The bedside clinical tests of the vestibular system are summarized in Table 2–3.[132,134,143,236,254,268,277,370,420]

CLINICAL FINDINGS WITH STATIC VESTIBULAR IMBALANCE

Initially inspect the eyes as the patient keeps the head stationary and fixes upon a distant point. Nystagmus may be present, particularly with acute vestibular imbalance. The hallmark of vestibular nystagmus is that it is initiated or accentuated when fixation is removed (see Box 10–1, in Chapter 10). (The effect of removal of fixation upon nystagmus is analogous to the Romberg test for postural instability in which case sway of the body increases on removal of vision.) During gentle eye closure, nystagmus may be seen as the lid ripples with each quick phase, or it may be palpated through the lids. A steady-state deviation of the eyes under closed lids may be inferred from the appearance of a corrective saccade back to primary position when the eyes are opened (see Video Display: Medullary Syndromes). Sometimes, horizontal vestibular nystagmus is induced during vertical smooth pursuit, perhaps because a separate fixation mechanism is turned off. In some patients, vestibular nystagmus is most apparent on upward gaze, perhaps because steady fixation is more difficult.

The effect of *fixation* on nystagmus also can be observed during ophthalmoscopy.[895] First, the patient fixes on a distant target with one eye while the examiner observes the optic disc of the other. Any drift of the optic nerve head is noted; then the fixing eye is covered for a few seconds in order to compare drift velocity with and without fixation. In interpreting the findings during ophthalmoscopy, it is sometimes easier to detect nystagmus by observing the slow-phase drifts, because the quick phases may be infrequent. Also, because the retina is behind the center of rotation of the eye, the direction of horizontal and vertical movement is the opposite of the direction seen when viewing the front of the eye. Torsional nystagmus may be detected during ophthalmoscopy if movement of the vessels around both sides of the macula is observed; on one side, quick phases will be directed upward and, on the other, downward. Likewise, laterally directed quick phases will appear that change direction when one looks above and below the macula. A beat of torsional nystagmus may also be elicited in patients with a unilateral loss of function asking them to blink—the top pole of the slow phase rotates towards the paretic ear.[722]

Frenzel goggles also are used to study eye movements in the absence of fixation. The commercially available illuminated goggles are best, but expensive; an alternative is +20 diopter lenses mounted in a spectacle frame and fitted with side-blinkers. The room lights should be turned off and the lights of the goggles or a pen light (illuminating one eye behind the goggles) used to illuminate the eyes. The patient should not fix on the illuminating light bulbs, lest nystagmus be spuriously created by the retinal afterimages that they produce.[94] Fixation can also be removed by having the patient look at a blank white sheet of paper while the examiner peeks in from the side to see the effect of removal of fixation.

Table 2–3. **Clinical Tests of Vestibular Function**

Tests of Vestibular Balance	
Static imbalance	
Gaze stability	—during fixation
	—during ophthalmoscopy
	—behind Frenzel goggles
Dynamic imbalance	
Nystagmus following head-shaking	
Gaze stability with rapid head turns (impulses) or translations (heaves)	
Positional-induced imbalance	
Positional nystagmus	
Imbalance induced by other measures	
Tragal pressure	
Valsalva maneuvers	
Hyperventilation	
Mastoid vibration	
Sounds	
Tests for Abnormalities of Vestibulo-Ocular Gain	
Comparison of visual acuity with head stationary and during head shaking at above 2 Hz	
Ophthalmoscopic examination during head shaking at about 2 Hz	
Testing for Vestibular Nystagmus	
After sustained rotation for about 45 seconds, observation of post-rotational nystagmus, behind Frenzel goggles	
Bedside Caloric Testing	
Minimal ice water caloric stimulation, with Frenzel goggles	

CLINICAL FINDINGS WITH DYNAMIC VESTIBULAR IMBALANCE

In patients with vestibular symptoms, a dynamic vestibular imbalance can be elicited relatively easily using three maneuvers: single, rapid head turns or head 'impulses', sustained head shaking, and mastoid vibration. We will also discuss a variant of the head impulse test, the head 'heave' test, to assess the function of the utricle and the translational VOR. Examples of these tests may be viewed in the Video Display: Disorders of the Vestibular System.

A single rapid head turn—the head impulse maneuver or head impulse test—is perhaps the most effective method for detecting a complete loss of labyrinthine function at the bedside (see Video Displays: Cerebellar Syndromes and Disorders of the Vestibular System).[370,374] Ask the patient to fix upon a target, usually the examiner's nose, while you briskly turn the head from one position to another, horizontally or vertically. The hands of the examiner are applied over the side of the patient's head with the force largely being transmitted through the bottom of the palms over the patient's temples. The rotation should not be large (less than 15°), but should be abrupt and of high acceleration. If the r-VOR is working normally, gaze will be held steady; if not, a corrective saccade will be needed at the end of the head movement to bring the image of the target back to the fovea. An abnormal test result is another manifestation of Ewald's second law. In this case, high-acceleration and/or high-frequency head motion are not transduced as well when the nerve is being inhibited as when it is being excited. Hence, in the absence of one-half of a push-pull pair of canals, the response is defective when the head is rotated toward the side of a unilateral loss of function.

The head impulse test can also be used to evaluate individual coplanar pairs of the vertical semicircular canals using a combined vertical-roll motion,[42,209,371,497] or by turning the head (but not the trunk) to the right or left by 45° and then rotating the head in the pitch plane relative to the body (i.e., up and down). Just as for the horizontal canals, an Ewald's law for high-frequency, high-acceleration stimuli can be used to identify loss of function of a single vertical canal. Take for example, a complete unilateral loss of labyrinthine function on the left side. With the head turned to the right on the body, the left anterior and right posterior semicircular canals (SCC) will be maximally excited with a pitch (relative to the body) stimulus. A corrective saccade will be present with rapid rotation of the head downwards (impaired function of the left anterior canal). Conversely, if the head is turned to the left on the body, the left posterior and right anterior SCC will be maximally excited with the pitch stimulus and a corrective saccade will be present with rapid rotation of the head upwards (impaired function of the left posterior canal).

The head impulse test is best performed in the planes of a pair of canals: right anterior, left posterior (RALP), left anterior, right posterior (LARP), or in the case of the lateral canals, with the head down about 30°.[726] Defects are probably best appreciated if the stimulus direction and amplitude is unpredictable.[726] The head impulse test is most consistently positive when there is a complete loss of labyrinthine function involving the lateral canal. Frequently, however, the test can be positive with a partial loss of function, and rarely, even in the absence of any abnormality

on caloric testing.[672] When performed as an active test by patients who have a unilateral loss of function, the head impulse test may not be positive because the slow-phase gain is higher and also the corrective saccades occur earlier. The corrective saccades can become embedded in the earliest part of the response and are completed before the head stops moving. These early, embedded saccades are difficult to discern at the bedside.[96,652] Even with passive rotations the corrective saccades sometimes may be hard to see (see Video Display: Disorders of the Vestibular System). This is especially true in young subjects and subjects who have acquired their vestibular loss slowly.

The head *heave* test is used to evaluate the t-VOR. It is a variant of the head impulse test though in this case is used to evaluate the function of the utricle (see Video Display: Disorders of the Vestibular System). As with the head impulse test, the hands of the examiner are applied over the side of the patient's head with the force largely being transmitted through the bottom of the palms over the patient's temples. An abrupt, high-acceleration lateral movement of the head is imposed while the subject is instructed to look at the examiner's nose. A corrective catch-up saccade is looked for, which indicates the t-VOR is hypoactive. Because normal individuals usually show a hypoactive t-VOR and may require a corrective saccade, the finding of an asymmetrical response (as occurs in the first days after a unilateral loss of function) is most helpful.

Clinical testing for *head-shaking nystagmus* is a useful method for detecting an induced asymmetry of velocity storage that occurs after peripheral vestibular lesions, or an actual asymmetry in velocity storage that occurs with central lesions.[37,285,366,436,460,467,657] While wearing Frenzel goggles, the patient is instructed to vigorously shake the head for 10 to 15 seconds side to side though a large excursion is not necessary. Immediately afterwards an induced nystagmus is sought (see Video Display: Disorders of the Vestibular System). The procedure is then repeated for vertical head shaking. With unilateral, peripheral, vestibular lesions, asymmetry of velocity storage is induced because there is a greater peripheral input when the head rotates toward the intact side. (One form of Ewald's second law dictates that at high speeds the intact labyrinth will not be able to decrease its discharge below zero for head rotations toward the paretic side.) After horizontal head shaking, patients with unilateral peripheral lesions may show horizontal nystagmus, initially with slow phases directed toward the side of the lesion (contralateral quick phases). The pattern of nystagmus is influenced by head orientation relative to gravity,[642] as are other manifestations of the velocity-storage mechanism such as the VOR time constant and OKAN. After vertical head shaking, patients with unilateral loss of labyrinthine function may show a relatively less prominent nystagmus with horizontal slow phases directed away from the side of the lesion (ipsilateral quick phases). This "cross-coupled" response probably reflects an asymmetry in the contribution that the posterior semicircular canal normally makes to the horizontal VOR during vertical head shaking.[364] It is important to remember that with a loss of labyrinthine function on one side, a head-shaking induced nystagmus will only occur when there is an intact velocity-storage mechanism. Velocity storage may be so impaired in some patients with an acute complete loss of vestibular function on one side, or with additional involvement on the other side, that they do not show head-shaking nystagmus.[285] Following circular head shaking (the patient rotates the head in a circle, up and left, then down and right), normal subjects produce a predominantly torsional nystagmus, which is probably a post-rotatory nystagmus rather than a nystagmus arising from the velocity-storage mechanism.[366,387] Hence the absence of circular head-shaking nystagmus can be used to infer bilateral loss of vertical canal function. Torsional OKN may be quite asymmetrical in unilateral vestibular loss with a better response with the top poles of the eyes rotating toward the paretic labyrinth.[517]

Central vestibular lesions may cause inappropriate cross-coupling of nystagmus, usually a prominent vertical nystagmus (especially downbeat) after horizontal head shaking (see Video Display: Disorders of the Vestibular System).[467,579,853] This is likely related to storage of inappropriate upward slow-phase activity during horizontal head shaking,which is discharged when the head shaking stops producing a transient down beating nystagmus. An alternative explanation would be activation of the vertical velocity-storage mechanism (which has an inherent upward bias) by the horizontal inputs *per se*, which would then discharge after head shaking. In either case, baclofen, which abolishes velocity storage,[184] should prevent vertical nystagmus after horizontal head shaking. Central lesions also may produce an asymmetry in the horizontal velocity-storage mechanism, which itself can produce horizontal head-shaking nystagmus even though the peripheral vestibular inputs are balanced. (In this case, the asymmetry of velocity storage might be revealed by finding different time constants for vestibular rotations in opposite directions.)

Some patients with peripheral lesions may show head-shaking nystagmus with ipsilateral quick phases. The mechanism may be related to recovery nystagmus,[539] which usually refers to a change in direction of spontaneous nystagmus when prior adaptive rebalancing suddenly becomes inappropriately excessive, as peripheral function recovers (see below). Similarly, a recovery in dynamic function could make prior adaptive changes inappropriate, thus causing an asymmetry in inputs to the velocity-storage mechanism during head shaking. This would cause head-shaking nystagmus in an opposite direction to that usually seen with a peripheral lesion. Relating the direction of head-shaking nystagmus to the affected ear can be particularly confusing in Ménière's syndrome in which the direction can be related to excitation, paresis, or recovery.[37,450]

Vibration applied to the mastoid tip may also bring out nystagmus in patients with unilateral loss of function and occasionally in other conditions such as superior canal dehiscence or other types of fistulae.[265,380,455,571,623,654,776] In the case of a unilateral loss of function, vibration of either mastoid (because the vibration impulses are transmitted relatively symmetrically through the skull to both labyrinths) elicits a nystagmus with a slow phase toward the paretic ear, in essence acting like a hot water caloric stimulus to the intact labyrinth. Vibration of the neck muscles can also produce changes in the subjective visual vertical, which can be asymmetrical in patients with unilateral loss of labyrinthine function.[92,548] When vibration brings out a vertical nystagmus a central lesion should be sought (see Video Display: Disorders of the Vestibular System).

POSITIONAL TESTING IN PATIENTS WITH VESTIBULAR DISORDERS

Positional testing is a key part of the vestibular examination in all patients who complain of vestibular symptoms, since benign paroxysmal positional vertigo (BPPV) is such a common cause of dizziness and imbalance, especially when induced by postural changes or turning over in bed.[141] A distinction should be made between a paroxysm of nystagmus induced by rapidly placing the patient in specific head-hanging positions (positioning nystagmus), and nystagmus that persists while the patient is held in a static position (positional nystagmus).

First, perform the Dix-Hallpike maneuver. With the patient sitting, the head is turned (not tilted) about 45° toward one side. The examiner stands in front of the patient and holds the head at the temples. After informing and reassuring the patient of the nature of the test, the head, neck, and trunk are moved en bloc to a head-hanging position (see Fig. 11–4, Chapter 11), about 30° below the horizontal. After the initial positioning of the head in the upright position, there need be little change in the position of the head on the body, apart from making sure the head gets below earth horizontal. A variant ("side-lying") in which the patient turns to the side with the nose 45° away from the tested side may be easier to tolerate for older individuals, especially if they have neck problems.[191] Note the eye movements in primary position and on left and right gaze. After about 45 seconds or earlier if any induced nystagmus has stopped, return the patient to the upright position and observe the eye movements again. Repeat the whole procedure with the head rotated 45° toward the other shoulder. Transient mixed vertical-torsional nystagmus induced by these maneuvers is usually diagnostic of BPPV emanating from the posterior semicircular canal (see Video Display: Positional Nystagmus).

Testing for nystagmus with static changes in head position (e.g., with the subject lying supine, with the head turned to the right, and with the head turned to the left) is useful in eliciting the horizontal nystagmus associated with the lateral canal variant of BPPV. This nystagmus usually changes direction with lateral head turn (direction-changing nystagmus), such that it is either always beating toward the

earth (geotropic) or always beating away from the earth (apogeotropic). When there is a question of a positional nystagmus being caused by vertebral artery compression one can compare nystagmus induced with changing the orientation of the head with respect to the body with nystagmus induced during en bloc rotation of the body. Direction-changing nystagmus can occur with either peripheral or central vestibular lesions,[60,63,861] but the lateral canal variant of BPPV is probably the most common cause. Some normal subjects show a weak horizontal nystagmus with positional testing in darkness. It is usually in the same direction with respect to the head (direction-fixed nystagmus), whether the head is turned to the left or to the right. The clinical features of BPPV and other forms of positional nystagmus are discussed in detail in Chapter 11.

OTHER TECHNIQUES FOR TESTING PATIENTS WITH VESTIBULAR SYMPTOMS

Several other clinical maneuvers may be used to induce an inappropriate nystagmus. Tragal compression can be used to test for a fistula, or for abnormalities of the ossicular chain and its connection to the oval window. A pneumatic otoscope is a better way to apply pressure to the tympanic membrane. The Valsalva maneuver (tested against both the closed glottis and against pinched nostrils) may produce symptoms and signs in patients with craniocervical junction anomalies such as the Arnold–Chiari malformations or with perilymph fistula or canal dehiscence syndromes.[687] A change in direction of the nystagmus during a Valsalva performed with pinched nostrils, versus with a closed glottis, is characteristic of the superior canal dehiscence syndrome. Hyperventilation may precipitate nystagmus in patients with a variety of lesions including compensated peripheral lesions,[713] fistulas, and compressive lesions on the vestibular nerve[582] including tumors (see Chapter 12, Case History: Hyperventilation-Induced Nystagmus, and Video Display: Disorders of the Vestibular System). Central lesions such as abnormalities at the craniocervical junction or demyelination may also produce hyperventilation-induced nystagmus. Hyperventilation may, of course, bring out manifestations of an anxiety syndrome, but without any nystagmus. An audiometer can also be used to look for sound-induced nystagmus (the Tullio phenomenon, see Video Display: Disorders of the Vestibular System).[580]

The ability to perform VOR suppression using visual fixation, either during caloric stimulation or combined eye-head tracking of a moving target (cancellation of the VOR), is a test of smooth pursuit (see Chapter 7). Note that patients who have intact VOR cancellation but impaired smooth pursuit may have a decreased VOR response (and hence have nothing to cancel when they track a target moving with their head).[574]

Vestibular nystagmus can be elicited by rotating the patient in a swivel chair at an approximately constant velocity (per-rotatory nystagmus). The head can be positioned to induce nystagmus that is horizontal (head upright), vertical (head turned to one shoulder), torsional (looking up at the ceiling), or mixed vertical-torsional from a push-pull pair of vertical canals (head turned 45° to the right and then pitched back by 90°). If rotation is maintained for about 45 seconds, at one revolution every 3 seconds, and the chair is then suddenly brought to a halt, post-rotational nystagmus will be induced. If the patient wears Frenzel goggles to abolish visual references, the duration of post-rotational nystagmus can be estimated, in each plane. The normal presence of quick phases also can be confirmed.

CLINICAL TESTS OF VESTIBULAR GAIN

Disturbances of visual acuity due to abnormalities of vestibular gain are most satisfactorily tested by quantitative methods.[806] Nevertheless, a simple assessment is possible by measuring dynamic visual acuity during head rotations. Ask the patient to read the optotypes of a visual acuity card while you passively rotate the head (horizontally, vertically, and then in roll (ear to shoulder)) at a frequency of about 2 cycles per second. Dynamic visual acuity is more degraded by head motion when viewing at near than at far,[662] and may diminish with age, especially in the vertical plane.[724] Encourage the patient not to stop at the turn-around points to prevent vision of the chart as the head slows down. If vestibular gain is abnormal, visual acuity will deteriorate by several lines compared with what the patient can read with the head still. Note that roll movements of the head do not usually lead to a significant decrease in visual acuity when labyrinthine function is lost, because foveal acuity is relatively independent of rotation of the eye around its visual axis. Thus, patients with factitious symptoms may report a marked decrease in visual acuity during roll as well as horizontal and vertical rotation of the head.

In some patients who have an abnormal gain of the r-VOR, it may be possible to detect corrective saccades during sinusoidal head rotation at a variety of frequencies (e.g., 0.5–2.0 Hz) during attempted fixation upon a target (see Video Display: Disorders of the Vestibular System); these saccades may be more apparent during fixation of a near target (e.g., at 15 cm). If the gain is too low, saccades will be directed opposite to the movement of the head; if the gain is too high, the converse occurs.

A more sensitive bedside assessment of the gain of the r-VOR can be made using the ophthalmoscope.[895] While the examiner views one optic nerve head and vessels, the patient is asked to view a distant target and shake the head from side to side. At frequencies greater than about 2 cycles per second, the pursuit system alone is unable to hold images stable upon the retina; consequently at this frequency gaze stability depends solely upon the VOR. The fixing eye can also be covered during head shaking to eliminate visual cues to pursuit. Recall that because the retina is behind the center of rotation of the eye, the direction of horizontal or vertical movement is the opposite of what is seen when viewing the front of the eye. If the gain of the VOR is unity, then the position of the eye with respect to the observer (eye in space) is stable, since eye movement in the orbit is equal and opposite to head movement in space: the optic nerve head and retinal vessels appear stationary. If the vessels or disc appear to move opposite to the direction of the head, then the reflex is hypoactive (gain less than 1.0); if they move in the same direction, then the reflex is hyperactive (gain greater than 1.0). If the nerve head drifts in the same direction regardless of the direction of head movement, there is a directional preponderance caused by vestibular imbalance. In the unconscious patient, visual systems are in abeyance, and once again the vestibular system can be studied in isolation, using rapid head turns or the ophthalmoscope test (see also Chapter 12).

Recall that patients who habitually wear a spectacle correction may adaptively change the gain of their VOR. The results of the ophthalmoscope test must be interpreted accordingly: the gain goes up with a hyperopic correction, and down with a myopic correction. Finally, patients with essential head tremor and vestibular failure may show abnormal oscillations during ophthalmoscopy,[146] and decreased visual acuity.[891]

BEDSIDE CALORIC TESTING

Caloric testing is often valuable in determining the side of a peripheral vestibular lesion. After verifying that the tympanic membrane is intact and that wax is absent, the minimal ice water caloric test may be performed.[611] The patient's head should be elevated 30° relative to earth-horizontal, to place the lateral semicircular canal in a vertical position. This ensures that thermally induced changes in the density of the endolymph lead to a maximal deflection of the cupula. Ideally, eye movements should be observed behind Frenzel goggles or recorded in darkness, to avoid the effects of visual fixation. A normal response can be elicited with as little as 0.2 mL of ice-cold water. Being essentially a low-frequency stimulus, caloric testing can detect vestibular impairment that may not be apparent during higher-frequency head rotation.[61] Conversely caloric testing may be in the normal range when head rotations are abnormal.[672]

LABORATORY EVALUATION OF VESTIBULAR AND OPTOKINETIC FUNCTION

By recording movements of the eyes, it is possible to quantify the vestibulo-ocular and optokinetic responses. Some methods available for testing vestibular and optokinetic responses are listed in Table 2–4; methods for recording eye movements are summarized in Appendix B.

In quantifying the performance of the VOR, the goals of testing are to determine VOR gain, phase, and imbalance. A static vestibular imbalance is manifest by spontaneous nystagmus and is best detected by recording eye movements in the absence of fixation (see Box 10–1, in Chapter 10). Such nystagmus may

Table 2–4. **Laboratory Evaluation of Vestibular Function**

VESTIBULO-OCULAR REFLEX (SEMICIRCULAR CANALS)	
Quantitative Caloric Testing	
Rotational Testing	
Passive rotation:	Sinusoidal
	Velocity steps
	Pseudo-random
	Accuracy of "gaze-adjusting" saccades
Active head shaking: sinusoidal or sudden head turns (position steps)	
OPTOKINETIC SYSTEM	
Measurement of OKAN, in darkness, following varying periods of full-field optokinetic stimulation	
OTOLITHIC-OCULAR REFLEXES	
Linear acceleration on moving platform, sometimes combined with rotations, giving six degrees of freedom	
Human centrifuge	
Passive change in tilt (roll) (up to 360 degrees)	
Rotation about an axis tilted from earth-vertical (e.g., OVAR or "barbecue-spit")	
Rotation of body about earth-vertical axis with head positioned eccentrically (e.g., forward or to side of the axis of rotation)	
Parallel swing	
Linear carts	
Subjective visual vertical (and horizontal)	

follow Alexander's law and can be classified as first degree (present only when looking in the direction of quick phases), second degree (also present in primary position), and third degree (present in all directions of gaze). In some patients, the nystagmus may reverse direction between right and left gaze. The effects of different gaze positions upon vestibular nystagmus probably relate to interactions between a vestibular imbalance and the gaze-holding network (neural integrator) (see Chapters 5 and 10).

Quantitative Caloric Testing

Laboratory caloric testing[168,373,656] is useful for detecting loss of peripheral vestibular function.[302] Introduced by Bárány, the method was standardized and popularized by Fitzgerald and Hallpike. The caloric response is due to two separate effects of the thermal stimulus: convection currents induced in the endolymph, and a direct effect of the temperature change on the discharge rate of the vestibular nerve; the convection currents are more important.[632]

Caloric responses are best tested with the subject in complete darkness or wearing Frenzel goggles in a dark room. It is important to maintain the state of arousal of the subject with an alerting stimulus such as vocalization.[855,872] The head of the supine subject is tilted upwards by 30°; thermal gradients then principally stimulate the lateral semicircular canals, since the canals are approximately vertical in this head position. Traditionally, water is infused into the external auditory meatus at temperatures of 30° and 44°C, although air also may be used. After checking that the tympanic membranes are intact, the procedure typically consists of first infusing 250 mL of water at 44°C for 40 seconds into one ear and recording the ensuing nystagmus. After a recovery period of 5 minutes, the same stimulus is repeated for the opposite ear. Then each ear is stimulated, in turn, with water at 30°C. Shorter versions of the test have been advocated, often using simultaneous bilateral stimulation, or bithermal stimulation (hot immediately followed by cold or vice versa).[72] In analyzing the nystagmus induced by caloric stimulation, maximum horizontal slow-phase velocity is considered the most reliable index of peripheral vestibular function. Each laboratory should establish its own range of normal values because the conditions of testing are partly responsible for the variability of results. Curiously, age has been reported to have little impact on caloric responses, though rotational testing results are affected by age (see above).[527]

If both warm and cold stimuli produce less response in one ear than in the other, and this asymmetry is 25% or greater, then a unilateral peripheral vestibular disturbance (often called canal paresis) is likely. When caloric stimuli cause a greater ocular response in one direction (e.g., greater slow-phase velocities—to the left—from warm water in the right ear and cold water in the left ear, than slow-phase velocities—to the right—produced by the opposite stimuli), there is a directional preponderance of the vestibular system. If the asymmetry of leftward and rightward slow phases exceeds 30%, then the directional preponderance is likely to be significant. Directional preponderance occurs with both peripheral and central vestibular lesions; by itself, it has no localizing value.[373] Some normal subjects and patients with vestibular symptoms may show a vertical (usually downbeating) component to their caloric-induced nystagmus. Provided that there is a horizontal component (so that the nystagmus is oblique), this appearance is not necessarily abnormal.[69]

In a few laboratories more sophisticated caloric testing is performed. Caloric testing can be modified to simulate a rotational stimulus and information about the time constant of the VOR and any adaptive responses can also be obtained.[291] Furthermore a three-dimensional analysis of caloric nystagmus with the head in different orientations can be used to evaluate the function of each of the semicircular canals and to infer interactions between the otoliths and the semicircular canals.[46,47,661]

Quantitative Rotational Testing

Rotational tests give more accurate and reproducible results than do caloric tests, though, of course, they have the disadvantage of not being able to stimulate a single labyrinth alone.[302] The alertness and mental state of the patient while in darkness may influence the results. Testing should be performed with the eyes open, in darkness;[855] if this is not possible, patients should gently vocalize (e.g., count aloud) while their eyes are closed.[536,872] VOR gain may be obtained by measuring the peak eye velocity in response to a velocity step (e.g., sudden sustained rotation at 50 or 100 degrees per second). The gain of the VOR also can be measured during sinusoidal rotation; consideration should be given to the distance at which a visual (or remembered) target is fixated, since this will affect gain (see Laboratory Evaluation of Eye-Head Movements, in Chapter 7). Rotational testing also can reveal asymmetry (or directional preponderance), in which the gain of the VOR is greater in one direction than in the other.[314]

The time constant of the r-VOR can be estimated from the phase shift at low frequencies of sinusoidal rotation. When the phase shift is 45°, the time constant is equal to the reciprocal of the frequency, expressed in radians per second. For velocity-step stimuli, the time constant can be estimated in several ways, assuming the decay is a simple exponential. One method is to use the logarithm of slow-phase velocity as a function of time. As a rough approximation, the time constant of the VOR can be estimated from the time that it takes slow-phase velocity to drop to 37% of its initial value (Fig. 2–7). Alternatively, one can measure cumulative slow-phase eye position (by adding up all the slow phases of the response) and then compute the time constant of the VOR from the ratio of cumulative slow-phase eye position to the initial value of slow-phase velocity (at the onset of the response).

At low frequencies (less than 0.01 Hz) of passive rotation in a vestibular chair, gain and phase relationships reveal information about peripheral vestibular disease. The time constant is often decreased in such patients (to values less than 10 seconds), but repetitive low-frequency stimuli can themselves shorten the VOR time constant because they habituate the response. Nevertheless, low-frequency stimuli are useful for revealing peripheral vestibular loss.[61,600]

An asymmetry of the vestibular responses due to unilateral labyrinthine disease (even involving just one semicircular canal) is more easily demonstrated with either head accelerations exceeding 2000 degrees per second,[42,43,370,371] or head velocities exceeding 100 degrees per second.[64,705] It is generally easier to apply such stimuli with a manual head turn than with a vestibular chair. Deficits in function of the lateral canals can also be demonstrated if high-speed rotations of the chair are applied with the head pitched forward 30°, so as to stimulate maximally the lateral semicircular canals. In this way rotation toward the paretic side is more likely to reveal an abnormality.[818] By recording the rotation of the eye around all three axes (horizontal, vertical, and torsional), in response to different patterns of head rotation that maximally stimulate differ-

ent pairs of canals, the function of individual canals can be evaluated and pathology can be more precisely localized to an individual semicircular canal or a combination of canals.[45,209,280,292,370,882] Pseudorandom (white noise) chair rotations offer a broad bandwidth of stimulus frequencies and short testing time and negate effects of prediction on the VOR. They require substantial instrumentation and analysis programs, however.

Another simple way to test the VOR uses the presence of corrective saccades and does not require precise measurement of slow-phase eye movements.[733] The patient views an earth-stationary target; then the lights are turned off and the chair is briefly turned. The patient is required to keep looking at the remembered target location. Normal subjects show a combination of a vestibular slow phase and usually a small gaze-adjusting saccade. The lights are then turned on and any inadequacy of the combined vestibular-saccadic response that occurred in darkness is revealed by a corrective saccade that brings the fovea to the target. Although the response during this test is the sum of a slow phase and a saccade, vestibular and other sensory inputs are essential in programming the size of the saccade. The test may be a sensitive way of detecting vestibular imbalance.[732] A similar strategy can be used to assay otolith function during translation of the body,[89] though this has not yet been applied clinically.

Active head rotation is a convenient way to test for unilateral labyrinthine lesions.[242,616] Caution is required, however, in equating eye movements generated during active head rotation with the passively induced VOR.[499] Especially in patients with bilateral vestibular loss, active head rotation tests not only the VOR but also preprogrammed eye movements and the contribution of the cervico-ocular reflex (see Video Display: Disorders of the Vestibular System). Abnormalities of gain and phase during high-frequency (2 Hz–6 Hz), active head movements have been reported to be at least as sensitive as caloric testing in detecting unilateral vestibular hypofunction,[619,711] or abnormalities in Ménière's syndrome.[409,615] Active pitch head rotations may not be as effective in detecting disturbances of individual vertical semicircular canals;[325] canal plane stimulation using non-predictable passively imposed head impulses is probably the best way.[242,243] Active head rotations have also been used to monitor the progress of patients undergoing physical therapy for vestibular loss due to ototoxicity, for example.[96,618]

Other ways to test the VOR, and especially to distinguish end organ from nerve involvement, or canal from otolith involvement, include galvanic stimulation[263,295,440,441,525,597,742] and recording of vestibular-evoked and sound-evoked potentials.[192,375,378,447,463,516,597,598,742,812,874,908] With the exception of recording sound-induced myogenic potentials in the neck muscles as a measure of saccule function (vestibular evoked myogenic response (VEMPs)), which is useful in the diagnosis of superior canal dehiscence or large vestibular aqueduct syndrome, these galvanic stimulation and evoked potential methods are rarely used in a routine clinical setting.

Optokinetic Testing

Optokinetic testing requires a stimulus that fills the field of vision. A common method is for the patient to sit inside a large, patterned optokinetic drum. Virtual reality (VR) technology has been used to overcome the cumbersome nature of large mechanical rotating drums.[479] Another method is to rotate the patient at a constant velocity for more than a minute with the eyes open in an illuminated room; as the labyrinthine signal dies away, the sustained nystagmus is due to purely visual drives. Small hand-held optokinetic drums or tapes primarily test the pursuit system. The optokinetic response is judged by both the nystagmus during visual stimulation (which in primates consists of pursuit and optokinetic components), and the optokinetic after-nystagmus (OKAN) that occurs after the lights are turned out (Fig. 2–7). The instructions to the patient influence the pattern of nystagmus quick phases during optokinetic stimulation.[817] If the patient is asked to follow the stripes, there are prolonged slow phases with large corrective saccades (look nystagmus). If the patient is asked to stare straight ahead as the stripes pass by, quick phases are smaller and more frequent (stare nystagmus).

The velocity-storage component of the optokinetic system is best evaluated by measuring OKAN, though this can be a somewhat feeble and variable response in many subjects. The initial slow-phase velocity of OKAN, after a 60-second period of stimulation, ranges from 6 degress per second to 20 degrees per second, and right-left asymmetry does not exceed about 6 degrees per second.[808] As previously discussed, the initial velocity of OKAN and its time constant vary considerably, so several measurements should be made for each patient. A convenient method is to sample the buildup of the slow-phase velocity of OKAN during frequent, 2-second periods of darkness during stimulation.[288,734] These periods are too short to discharge the velocity-storage mechanism. It is important to discard data from the first second of each of these 2-second epochs, to prevent contamination by the influences of the pursuit system.

Testing Otolith-Ocular Responses

Testing of otolith-ocular function in humans has traditionally been relegated to a few sophisticated laboratories because it usually requires elaborate equipment such as moving platforms or parallel swings that impose linear acceleration, human centrifuges, or special chairs that rotate the subject around the roll axis (to test ocular counterroll).[348,350,633,649] Recently, however, several more practical tests of otolith function have been introduced.[134,370,685] Measures of the subjective visual vertical or subjective visual horizontal can be used to infer the torsional position of the eye, and hence imbalance in otolith-ocular reflexes,[85,110,259,362,844] and can be carried out in the clinic with a hand-held laser fitted with inexpensive line-generating optics.[741] The functional integrity of the saccule and of its afferents carried in the inferior division of the vestibular nerve, can be tested using clicks or head vibration (with a reflex hammer) as the stimulus, and measuring the response in the surface EMG activity of the sternocleidomastoid—which is a sacculo-collic reflex.[193,370,379,596,702,875] For example, patients with vestibular neurolabyrinthitis who develop BPPV have a normal click-evoked neck EMG, confirming sparing of the inferior division of the vestibular nerve.[596] Conversely, these potentials are abnormal in inferior vestibular neuritis.[372]

Tilt-suppression of post-rotatory nystagmus (the subject's static head position is reoriented with respect to gravity at the beginning of post-rotatory nystagmus) is a test of the ability of the nodulus to modulate the velocity-storage mechanism. It uses a change in otolith activity to signal a change in orientation of the head with respect to gravity.[282] Tilt-suppression is abnormal with nodulus lesions (Box 12–3, Chapter 12).[369]

It may be possible to identify the side of an acute utricular lesion by measurement of the asymmetry of torsional eye movements (ocular counterrolling) during lateral head tilt,[250] or changes in torsion or in the perception of tilt of a light-bar (oculogravic illusion) during imposed linear acceleration in a human centrifuge.[221,228] During yaw axis rotation one can look for an asymmetry in utricular function by placing the axis of head rotation first though one labyrinth and then the other, and measuring ocular counterroll or displacement of the subjective visual vertical.[176]

The translational VOR (t-VOR) , as measured during an abrupt, high-acceleration lateral movement of the head (head 'heave') may be asymmetrical with an acute unilateral lesion with a lesser response when the head is moved toward the side of the lesion (probably reflecting a form of Ewald's second law for the otoliths).[29,31,503,504,617,685] The t-VOR also shows a loss of modulation with viewing distance. Chronically, asymmetries are much less in the t-VOR than r-VOR, though the t-VOR gain may be reduced bilaterally.[49,206,504,685] In monkeys, abnormalities of the tVOR following unilateral loss of function are more prominent and enduring during fore-aft stimulation with abnormally directed slow phases when the eyes are directed toward the side of the lesion.[31] The effect of otolith stimulation also can be measured during sustained rotation about an axis tilted from earth vertical (OVAR), which in the extreme case is about an earth-horizontal axis and is called barbecue-spit rotation (see OVAR above). Another method is to rotate the subject about an earth-vertical axis with the head positioned in front of the center of rotation of the chair in which the subject sits (eccentric rotation);[49,207,354,738] such a stimulus causes the gain of compensatory eye

movements to increase, especially if the subject views or imagines a near target. In some patients, this enhancement of gain with eccentric head position has been found to be absent; in others, asymmetries appeared that were not evident with the head centered. The practical role of these types of rotational testing in evaluating otolith dysfunction is not yet established.

PATHOPHYSIOLOGY OF DISORDERS OF THE VESTIBULAR SYSTEM

Disorders of the peripheral or central vestibular system disrupt eye movements, following the pathophysiological principles summarized in Table 2–5. In Chapter 11, we discuss these abnormalities from a viewpoint of topological diagnosis.

Pathophysiology of Acute Unilateral Disease of the Labyrinth or Vestibular Nerve

Acute, unilateral vestibulopathy causes a static imbalance of vestibular tone; the difference in neural activity of the left and right vestibular nuclei causes spontaneous nystagmus (Box 10-1, Chapter 10). For example, unilateral loss of an entire labyrinth or destruction of the vestibular nerve causes a mixed horizontal-torsional nystagmus, with slow phases directed toward the side of the lesion. The pattern of nystagmus reflects the summed influence of individual semicircular canals on one side (Fig. 2–2A). Disease restricted to a single canal or its immediate projections causes nystagmus in the plane of that canal, independent of the position of the eye in the orbit. So, for example, disease of the left posterior semicircular canal causes a nystagmus that appears more vertical on looking to the right and more torsional on looking to the left; the eyeball rotates approximately in the same plane in the head, irrespective of the direction of the line of sight. This pattern of nystagmus is commonly encountered in benign paroxysmal positional vertigo (see Video Display: Positional Nystagmus).[211]

Table 2–5. **Disorders of the Vestibular-Optokinetic System**

Type of Disorder	Features
Unilateral peripheral vestibular disorders	Static imbalance of canal inputs causing spontaneous nystagmus
	Dynamic imbalance with lower gain for horizontal head rotations or head translations, at high velocity or high accelerations, towards the side of the lesion
	Loss of velocity storage causing reduced r-VOR time constant
	Imbalance of otolith inputs causing skew deviation; positional nystagmus
Bilateral peripheral vestibular disorders	Severest impairment of gain is usually for low-frequency stimuli
	VOR time constant shortened to less than 6 seconds
	Loss of OKAN
	Loss of response to circular head shaking
Central vestibular disorders	Imbalance of canal connections causing nystagmus that is often purely vertical or purely torsional
	Imbalance of otolith connections causing skew deviation
	Increased or decreased r-VOR gain
	Prolonged or shortened r-VOR time constant
	Decreased t-VOR gain
Optokinetic disorders	Loss of OKAN with peripheral vestibular lesions
	Slow buildup of OKN with lesion affecting various parts of the visual pathways
	Asymmetric, monocular OKN in individuals who have not developed binocularity

OKAN, optokinetic afternystagmus; VOR, vestibulo-ocular reflex; r-VOR, rotational VOR; t-VOR, translational VOR.

Disease of the *superior division* of the vestibular nerve—which is usually due to viral infections—also produces a distinctive pattern of nystagmus. Patients show a mixture of horizontal, vertical (slow phase downward), and torsional nystagmus that is compatible with involvement of the anterior and lateral semicircular canals.[41,278] Similarly, selective involvement of the *inferior division* of the vestibular nerve can be identified, often with an accompanying loss of hearing, due to involvement of the cochlea, and abnormal sound-induced VEMP due to involvement of the sacculus.[40,372,596] Rarely, the slow phases of spontaneous nystagmus are directed away from the side of the lesion; in some cases, this may represent a compensatory mechanism and has been called recovery nystagmus (discussed above).

A *dynamic vestibular imbalance* the VOR, affecting gain and time constant, is also produced by a unilateral loss of labyrinthine function. In labyrinthectomized monkeys, the VOR gain initially falls from a preoperative value of about 1.0 to approximately 0.5 and the time constant of the VOR declines from 35 seconds to about 7 seconds.[282] The decline in the time constant represents loss of velocity storage, which is also evident from a loss of OKAN, particularly following optokinetic drum rotations toward the side of the intact ear. In addition, the VOR is asymmetric (directional preponderance), partly owing to the spontaneous nystagmus. When correction is made for the spontaneous nystagmus, however, VOR gain is still lower for high-speed head rotations toward the side of the lesion. This finding is consistent with Ewald's second law. Similar changes are found in humans with unilateral labyrinthine loss,[136,365,367,789] although even at lower head velocities there may be some asymmetry of response.[315] Some recovery of these dynamic disturbances occurs if monkeys are kept in an illuminated environment: VOR gain increases towards a value of 1.0 and the time constant of the VOR rises slightly (to about 9 seconds). At higher head velocities, however, VOR gain remains lower than preoperatively (approximately 0.8) and is asymmetric, being lower for head rotations toward the side of the lesion. A similar course of recovery has been reported in humans who suffer unilateral labyrinthine loss,[62,150,279,285,353,399,445,655] although with high accelerations the recovery of the rotational VOR is considerably more limited.[44,45,209,719,807] Another finding with unilateral loss is hypometria of gaze-adjusting saccades following ipsilateral head turns.[732]

If the other labyrinth is destroyed after recovery from a unilateral labyrinthine lesion, a deficit occurs as if the original damaged labyrinth were intact. This *Bechterew's phenomenon* reflects the rebalancing of central vestibular tone following the first lesion. The second lesion then creates a new imbalance and reflects the actions of *adaptive mechanisms* in a similar way to the adaptive rebalancing mechanism that underlies the appearance of *recovery nystagmus*.[459,899]

Unilateral disease of the vestibular organ also may cause imbalance of otolith function.[134,176,352,354] Sometimes there is a prominent ipsilateral head tilt, and an ocular skew deviation in which the eye ipsilateral to the lesion is lower and extorted; the contralateral eye is higher and intorted. This is the ocular tilt reaction (OTR).[126,129,312,376,725] The torsion can also be detected objectively, or by measurements of the subjective visual vertical or horizontal.[85,109,110,218,221,362,435,785,834] This pathological skew and torsion is quite different from that produced physiologically by static head tilt in normals.[93,197,844] Pathological skew resembles the otolith imbalance produced by experimental stimulation of the utricle in lower animals (Fig. 2–2B). In lateral-eyed animals, a skew deviation of the eyes is the appropriate response to a lateral head tilt. Even in normal human subjects,[384,442,572,646] and in monkeys,[739] a small amount of dynamic skewing may be associated with rolling the head. The amount of skewing is influenced by the location of the point of regard. There may also be a pathological ocular torsion with a presumed lesion of a vertical semicircular canal alone, but in this case there is no displacement of the subjective visual vertical, implying that a perception of tilt requires a veridical signal from the otoliths

about the orientation of gravity relative to the head.[777]

Otolith inputs also may interact centrally with the connections of the semicircular canals. For example, it has been suggested that the reason that patients with an acute labyrinthine lesion often lie with the affected ear up is to use otolith inputs to decrease the imbalance between the canals, and so reduce nystagmus and discomfort.[290] A possible reason for this effect is that the change in the attitude of the head with respect to gravity (which calls for ocular counterroll) may be misinterpreted as a translation of the head away from the ground (which calls for a horizontal nystagmus with slow phases directed toward the intact labyrinth), which in turn could nullify the spontaneous nystagmus. As discussed earlier in this chapter, recent physiological studies emphasize the importance of semicircular canal signals in allowing a distinction between utricular activation by linear acceleration during lateral head tilt (which calls for ocular torsion) and utricular activation by lateral head translation (which calls for horizontal eye motion).[345,911] One can envision that if signals about head translation and head tilt are misinterpreted, as might be the case with a unilateral vestibular imbalance, there could be a diminution or enhancement of any spontaneous nystagmus depending upon the particular pattern of canal-utricular imbalance. In support of this idea is the finding that head-shaking nystagmus in patients with a unilateral peripheral neuritis is modulated by the static attitude of the head, being worse with the affected ear down.[642]

A dynamic otolith imbalance, following experimental unilateral otolith lesions, has been demonstrated in monkeys.[788] Acutely, the increase in gain of the VOR that is normally produced if the animal's head is positioned in front of the axis of rotation is no longer present. Recovery occurs in weeks. In humans with unilateral lesions, during off-vertical axis rotation (OVAR), with the body and axis of rotation tilted together away from upright (including earth-horizontal or barbecue-spit rotation), there is an abnormally low-amplitude or even inappropriately directed bias component when the head is rotated toward the lesioned side.[233,310,649] The modulation component is intact. Patients with a recent (one week) unilateral loss of labyrinthine function show a decreased response when their head is translated toward the abnormal side.[503,504,617] This may reflect the equivalent of an Ewald's law for the otolith response. Patients with more chronic lesions, however, usually show little asymmetry in the translational VOR though the responses to linear accelerations as high as 1*g* have not usually been investigated.[49,206,504] As discussed previously it has been suggested that the lateral portion of the utricle may respond best to translations (perhaps high-frequency linear acceleration stimuli that produce horizontal eye rotations) and the medial portion to the pull of gravity (perhaps low-frequency linear acceleration stimuli that produce torsion). This would account for the seeming paradox that patients with a unilateral loss of labyrinthine function have a deficit in the translational VOR when moving toward the lesioned side, and abnormal ocular counterroll when tilted toward the side of the lesion.[354]

In sum, there are a number of ways to diagnose unilateral labyrinthine hypofunction, and using the latest physiological understanding of vestibular function with important technical advances now allow for testing each of the individual components of the rotational and translational VOR. Head impulse and head heave testing in the correct planes of motion probe the function of each of the semicircular canals and of the utricle, while vestibular evoked myogenic potentials probe the function of the saccule.

Pathophysiology of Bilateral Loss of Vestibular Function

Bilateral labyrinthine loss presents a sensory deficit to which the brain cannot so readily adapt. In the acute phase of loss of labyrinthine function, the inadequate VOR causes visual images to move on the retina with every head movement; this causes oscillopsia and impairment of vision (see Video Display: Disorders of the Vestibular System). Some clinical causes of bilateral vestibular loss are included in Table 11–3, Chapter 11. Patients with partial, bilateral vestibular loss may show preferential sparing of the r-VOR for high-frequency stimuli;[61] testing with lower-frequency rotations or caloric stimuli are more likely to demonstrate the deficit though the converse is occasionally true.[672] With time, a number of strategies may

be developed to compensate for this deficit (see Table 7–1, Chapter 7).[458] These include potentiation of the cervico-ocular reflex, preprogramming of compensatory eye movements, substitution of small saccades and quick phases in the direction opposite head rotation to augment inadequate vestibular slow phases, improvement of smooth pursuit, restriction of head movement, and perceptual threshold changes to ignore oscillopsia.[96,106,134,142,358,377,396,570,613,652,653,801] Because of these adaptive mechanisms, the gain of compensatory eye movements may be near normal during active head rotation. During less predictable head motions, however, such as those occurring during walking, it is harder to compensate for the deficit, and gaze instability causes impaired vision and sometimes oscillopsia. Like unilateral vestibular lesions, bilateral disease causes loss of velocity storage with a consequent shortening of the time constant of the r-VOR,[61] and of OKAN.[188,367,904]

Pathophysiology of Lesions of Central Vestibular Connections

Disturbance within central vestibular structures also may produce disturbances of balance, gain, direction and phase (time constant) of the VOR.[267,688] One way to approach these central disorders is to divide them into those that affect the different planes of rotation (roll, yaw, and pitch), which in turn have topographical diagnostic use.[130,253] Imbalance of otolith inputs and disturbance of optokinetic nystagmus may occur. Moreover, disturbance of gaze-holding function may be impaired because the medial vestibular nucleus is an important contributor to the neural substrate for gaze-holding (see Chapter 5). Central lesions may occasionally mimic isolated peripheral vestibular lesions, for example, infarction of the cerebellar nodulus[495,496] or pontine lesions.[797]

Imbalance of central vestibular tone leads to spontaneous nystagmus that is usually present in primary position. Examples discussed further in Chapter 10 are downbeat (Box 10–2), upbeat (Box 10–3), and torsional nystagmus (Box 10–4). Some cases of horizontal nystagmus also may represent imbalance of central vestibular connections. A number of hypotheses have been proposed to explain the pathogenesis of central vestibular nystagmus; these are discussed in Chapter 10. Experimental ablation of the flocculus and parafloccculus (Box 12–2, Chapter 12) invariably produces downbeat nystagmus, perhaps because these structures inhibit the VOR in an asymmetric pattern.[531,903] Purkinje cells from the flocculus send inhibitory projections to the central connections of the anterior canal but not to those of the posterior canal.[434] Downbeat nystagmus (see Video Display: Downbeat, Upbeat, Torsional Nystagmus) is commonly present in patients with the Arnold–Chiari malformation and other abnormalities at the craniocervical junction.

Experimental ablation of the nodulus and uvula in monkeys (Box 12–3, Chapter 12) causes prolongation of velocity storage and a loss of the normal ability to reduce post-rotational nystagmus by pitching the head forward when post-rotational nystagmus begins.[846] Humans with midline cerebellar tumors show a similar pattern of abnormality.[369] In addition, monkeys with nodulus lesions show downbeat nystagmus and defects in generating the bias component of OVAR.[19] They also develop periodic alternating nystagmus when in darkness (Box 10–5, Chapter 10);[846] this nystagmus is discussed in Chapter 10 (see Video Display: Periodic Alternating Nystagmus). A patient with a new uvula lesion superimposed on a lesion in the vestibular nucleus developed a paroxysmal alternating skew deviation and spontaneous nystagmus, presumably due to a loss of inhibition upon the vestibular nuclei.[680]

Experimental unilateral lesions of the vestibular nuclei in monkeys do not produce purely vertical or horizontal nystagmus; it is mixed horizontal-torsional, mixed vertical-torsional, or pure torsional.[827] With lesions of the vestibular nerve root and caudal lateral parts of the vestibular nucleus, the horizontal component of slow phases is directed toward the lesion. When the superior vestibular or rostral medial vestibular nuclei are lesioned, the horizontal component of the slow phases is directed away from the lesion. Nystagmus with vestibular nucleus lesions is more persistent than that caused by labyrinthectomy. Some patients with central vestibular lesions, however, may manifest nystagmus that corresponds to the effects of stimulating one semicircular canal.[688] Wallenberg's syndrome (lateral medullary infarction) may cause mixed

horizontal-torsional nystagmus with slow phases directed towards the side of the lesion. Experimental lesions of the medial vestibular nuclei and nucleus prepositus hypoglossi, which are essential elements of the gaze-holding mechanism (neural integrator), cause a combination of deficits of gaze holding and vestibular imbalance. These interactions and their relationship to Alexander's law of nystagmus are discussed in Chapter 5.

Lesions of the cerebral hemispheres, such as hemidecortication, cause some dynamic imbalance of the r-VOR.[270,832] During rotation in darkness, a mild asymmetry of r-VOR gain is present, with greater values being obtained for eye movements away from the side of the lesion. This asymmetry is greater if the patient either imagines or views a stationary target,[746] but is absent for higher-frequency rotations (see Chapter 12). Central lesions may affect the vestibular nerve as it courses through the brainstem or in the medial vestibular nuclei itself, causing a unilateral caloric paresis, but not usually a complete paralysis.[293]

The gain of the VOR is variably decreased or increased with central lesions. For example, disease affecting the vestibular nucleus at the root entry zone may cause loss of vestibular function similar to that from a more peripheral lesion in the labyrinth. Thus, with an occlusion of the anterior inferior cerebellar artery (AICA), the vestibular disturbance can be due to a combination of central vestibular and peripheral labyrinthine dysfunction (see Video Display: Cerebellar Syndromes). Lesions involving the flocculus and parafloccculus may cause either an increase or decrease in vestibular gain.[903] Patients with cerebellar disease may show vestibular hyper-responsiveness (VOR gain greater than 1.0), often with an upward predominance, as well as inappropriately directed slow phases commonly with an upward component.[246,328,798,852-854,898,901] Lesions of the vestibulocerebellum cause an inability to adapt the gain of the VOR in response to new visual demands.[513,686]

Disturbances of the phase and the time constant of the r-VOR may occur with disease affecting a variety of central structures. Bilateral lesions of the medial longitudinal fasciculus (MLF) (bilateral internuclear ophthalmoplegia (INO)) cause reduced gain of the vertical r-VOR; in addition, slow-phase eye velocity lags head velocity.[690] The torsional and vertical VOR may be affected in unilateral INO by virtue of greater involvement of posterior versus anterior semicircular canal pathways owing to their anatomical separation.[210] Lesions of the MLF also impair the horizontal VOR because of weakness of the ipsilateral medial rectus muscle. The consequence of these disturbances of phase and gain are impaired vision and oscillopsia with head movements. The interstitial nucleus of Cajal may influence the phase relationships of both the vertical and torsional r-VOR,[297,689] but quantitative studies of the effects of restricted lesions of this nucleus on the VOR in humans are lacking.

Unilateral lesions of central otolith connections cause skew deviation and the ocular tilt reaction.[253,259,725] With lateral medullary lesions affecting the vestibular nuclei, such as Wallenberg's syndrome (lateral medullary infarction) (Box 12–1, Chapter 12), the head is typically tilted (i.e., rolled ear-to-shoulder) toward the side of the lesion, and there is a skew deviation with hypotropia and excyclotropia of the ipsilateral eye (see Video Display: Medullary Syndromes).[260,810] Certain complaints of these patients, such as perceived tilts of the environment, probably also represent central disturbance of otolith inputs. Unilateral MLF or midbrain lesions may cause a contralateral head tilt and ipsilateral hypertropia,[259,261] consistent with interruption of the crossed pathways that subserve otolith inputs (Table 2–2).

Disturbance of visual inputs, whether due to immaturity of the visual pathways,[873] albinism,[247] or blindness,[754] may affect the time constant and gain of the r-VOR. It seems likely that such visual information is passed to the cerebellum, because cerebellar lesions cause similar deficits of ocular motility.[501,900,902]

Pathophysiology of Disorders of the Optokinetic System

Abnormalities of the optokinetic responses (Table 2–5) are caused by peripheral and central vestibular disease and by both developmental and acquired lesions affecting the visual pathways.[66,318,319,829] In primates, optokinetic nystagmus (OKN) represents the responses of both smooth pursuit and optokinetic systems. The performance of the velocity-storage component of the optokinetic response is most reliably evaluated by studying optokinetic after-nystagmus (OKAN) in the dark.

Unilateral peripheral vestibular disease (see Box 11–1, in Chapter 11), particularly during the acute phase, may also cause a directional preponderance of OKN, with increased slow-phase velocity toward the side of the lesion.[121] Unilateral labyrinthine lesions reduce OKAN to both sides but more so with visual stimuli moving toward the intact side.[137] Torsional OKN is also asymmetrical after vestibular loss with relative perseveration of slow phases with top poles rotating toward the lesioned side.[517] Patients who have bilateral labyrinthine loss show normal nystagmus during the period of optokinetic stimulation, but afterward show no OKAN in darkness.[893,904] This finding supports the notion that OKAN in humans, as in other species, depends on normal central vestibular tone. Disease of central vestibular connections that impairs velocity storage may abolish OKAN as well as affect the VOR time constant, and the ability to distinguish tilt from translation.

SUMMARY

1. During head perturbations, such as those caused by natural activities, the vestibulo-ocular, optokinetic, and smooth pursuit systems work together to generate compensatory eye movements and so maintain clear vision of the environment. The rotational vestibulo-ocular reflex (r-VOR), relying on inputs from the semicircular canals, generates compensatory slow-phase eye movements, at short latency, during brief (high-frequency) head turns (Fig. 1–4). The translational vestibulo-ocular reflex (t-VOR), relying on inputs from the otolith organs, generates compensatory slow-phase eye movements, at short latency, during brief (high-frequency) head translations (Fig. 1–5). During translation and horizontal and vertical rotation, the VOR must be adjusted for the viewing distance of the target of interest; the gain (amplitude) of the VOR must increase for viewing near targets.
2. The VOR functions less well at lower frequencies of stimulation so that the optokinetic system and smooth pursuit supplement the VOR during sustained rotations (Fig. 2–7) or translations.
3. Otolith inputs—responding to the pull of gravity—also generate a change in the static torsional alignment of the eyes (ocular counterrolling) in response to sustained lateral tilt of the head.
4. Inputs from the semicircular canals, otolith organs, visual system, and somatosensors are combined centrally, in the vestibular nuclei, to give the brain's best estimate of the orientation and the motion of the head.
5. Stimulation of any one semicircular canal causes compensatory eye movements in the plane of that canal (Fig. 2–2). The semicircular canals are arranged in three pairs, one from each pair on either side. The vestibular nerve shows a resting discharge rate that is modulated up or down according to head motion. This organization maximizes vestibular sensitivity and provides the system with an opportunity to cope with the effects of unilateral disease.
6. The VOR is capable of considerable adaptation of its properties in response to visual demands. This is a form of motor learning that depends upon the vestibulocerebellum and its projection sites within the vestibular nuclei (Fig. 2–10). There are, however, limitations on adaptive capabilities, imposed by Ewald's second law, that are the basis for useful diagnostic maneuvers for clinical vestibular testing. There are also significant cognitive contributions to VOR adaptation implying important cerebral hemisphere inputs to lower-level vestibular adaptive mechanisms.
7. Testing of the VOR requires measurement of symmetry (balance), gain (ratio of eye movement to head rotation), direction of the eye movement relative to the head movement, and the temporal synchrony between head and eye movements (reflected by phase or time constant). A number of factors influence the gain of the VOR. These include mental set, viewing distance of a target, and habitual wearing of a spectacle refraction as well as the nature of the stimulus. Testing of the optokinetic system entails

measurement of optokinetic after-nystagmus (OKAN). Testing of otolith function requires linear acceleration of the subject's head, rotation about an axis tilted from the gravitational vertical, or measurement of ocular counterroll to sustained head tilt. A useful clinical test of static otolith function is measurement of the percept of subjective visual vertical.

8. Disorders of the VOR cause changes in gain, phase, direction, and balance. Abnormalities in the VOR are best elicited with motion of the head that exceeds the usual range of frequency, velocity, or acceleration to which we are subject in everyday life. Disorders of the optokinetic system are characterized by abnormalities of OKAN; they occur in diseases that affect the peripheral or central vestibular system. Otolith disorders produce static tilts of the head, ocular torsion, and skew deviation—the ocular tilt reaction.

REFERENCES

1. Abadi RV, Pantazidou M. Monocular optokinetic nystagmus in humans with age-related maculopathy. Br J Ophthalmol 81, 123–129, 1997.

1a. Abadi RV, Howard IP, Ohmi M, Lee EE. The effect of central and peripheral field stimulation on the rise time and gain of human optokinetic nystagmus. Perception 34, 1015-1024, 2005.

2. Adeyemo B, Angelaki DE. Similar kinematic properties for ocular following and smooth pursuit eye movements. J Neurophysiol 93, 1710–1717, 2005.

3. Adrian ED. Discharges from vestibular receptors in the cat. J Physiol (Lond) 101, 389–407, 1943.

4. Ahn SC, Lee CY, Kim DW, Lee MH. Short-term vestibular responses to repeated rotations. J Vestib Res 10, 17–23, 2000.

5. Akao T, Kurkin S, Fukushima K. Latency of adaptive vergence eye movements induced by vergence-vestibular interaction training in monkeys. Exp Brain Res 158, 129–132, 2004.

6. Akbarian S, Grüsser O-J, Guldin WO. Thalamic connections of the vestibular cortical fields in the squirrel monkey (Saimiri sciureus). J Comp Neurol 326, 423–441, 1992.

7. Anastasio TJ. Input minimization: a model of cerebellar learning without climbing fiber error signals. NeuroReport 12, 3825–3831, 2001.

8. Anastasio TJ, Robinson DA. Distributed parallel processing in the vestibulo-oculomotor system. Neural Computation 1, 230–241, 1989.

9. Anastasio TJ, Robinson DA. The distributed representation of vestibulo-oculomotor signals by brainstem neurons. Biol Cybern 61, 79–88, 1989.

10. Anastasopoulos D, Gianna CC, Bronstein AM, Gresty MA. Interaction of linear and angular vestibulo-ocular reflexes of human subjects in response to transient motion. Exp Brain Res 110, 465–472, 1996.

11. Anastasopoulos D, Haslwanter T, Fetter M, Dichgans J. Smooth pursuit eye movements and otolith-ocular responses are differently impaired in cerebellar ataxia. Brain 121, 1497–1505, 1998.

12. Angelaki DE. The physiology of the peripheral vestibular system: the birth of a field. J Neurophysiol 93, 3032–3033, 2005.

13. Angelaki DE. Eyes on target: what neurons must do for the vestibuloocular reflex during linear motion. J Neurophysiol 92, 20–35, 2004.

14. Angelaki DE, Dickman JD. Gravity or translation: central processing of vestibular signals to detect motion or tilt. J Vestib Res 13, 245–253, 2003.

15. Angelaki DE, Dickman JD. Premotor neurons encode torsional eye velocity during smooth-pursuit eye movements. J Neurosci 23, 2971–2979, 2003.

16. Angelaki DE, Green AM, Dickman JD. Differential sensorimotor processing of vestibulo-ocular signals during rotation and translation. J Neurosci 21, 3968–3985, 2001.

17. Angelaki DE, Hess BJ. The cerebellar nodulus and ventral uvula control the torsional vestibulo-ocular reflex. J Neurophysiol 72, 1443–1447, 1994.

18. Angelaki DE, Hess BJ. Inertial representation of angular motion in the vestibular system of rhesus monkeys. II. Otolith-controlled transformation that depends on an intact cerebellar nodulus. J Neurophysiol 73, 1729–1751, 1995.

19. Angelaki DE, Hess BJ. Lesion of the nodulus and ventral uvula abolish steady-state off-vertical axis otolith response. J Neurophysiol 73, 1716–1720, 1995.

20. Angelaki DE, Hess BJ. Three-dimensional organization of otolith-ocular reflexes in rhesus monkeys. I. Linear acceleration responses during off-vertical axis rotation. J Neurophysiol 75, 2405–2424, 1996.

21. Angelaki DE, Hess BJM. Inertial representation of angular motion in the vestibular system of rhesus monkeys. I. Vestibuloocular reflex. J Neurophysiol 71, 1222–1249, 1994.

22. Angelaki DE, Hess BJM. Adaptation of primate vestibuloocular reflex to altered peripheral vestibular inputs. II. Spatiotemporal properties of the adapted slow-phase eye velocity. J Neurophysiol 76, 2954–2971, 1996.

23. Angelaki DE, Hess BJM. Organizational principals of otolith- and semicircular canal-ocular reflexes in rhesus monkeys. Ann N Y Acad Sci 781, 332–347, 1996.

24. Angelaki DE, Hess BJM. Visually induced adaptation in three-dimensional organization of primate vestibulo-ocular reflex. J Neurophysiol 79, 791–807, 1998.

25. Angelaki DE, McHenry MQ. Short-latency primate vestibuloocular responses during translation. J Neurophysiol 82, 1651–1654, 1999.

26. Angelaki DE, McHenry MQ, Dickman DJ, Newlands SD, Hess BJ. Computation of inertial motion: neural strategies to resolve ambiguous otolith information. J Neurosci 19, 316–327, 1999.

27. Angelaki DE, McHenry MQ, Dickman JD, Perachio AA. Primate translational vestibuloocular reflexes. III. Effects of bilateral labyrinthine stimulation. J Neurophysiol 83, 1662–1676, 2000.

28. Angelaki DE, McHenry MQ, Hess BJ. Primate translational vestibuloocular reflexes. I. High-frequency dynamics and three-dimensional properties during lateral motion. J Neurophysiol 83, 1637–1647, 2000.

29. Angelaki DE, McHenry MQ, Newlands SD, Dickman JD. Functional organization of primate translational vestibulo-ocular reflexes and effects of unilateral labyrinthectomy. Ann N Y Acad Sci 871, 136–147, 1999.

30. Angelaki DE, Newlands SD, Dickman JD. Inactivation of semicircular canals causes adaptive increases in otolith-driven tilt responses. J Neurophysiol 87, 1635–1640, 2002.

31. Angelaki DE, Newlands SD, Dickman JD. Primate translational vestibuloocular reflexes. IV. Changes after unilateral labyrinthectomy. J Neurophysiol 83, 3005–3018, 2000.

32. Angelaki DE, Perachio AA. Contribution of irregular semicircular canal afferents to the horizontal vestibuloocular response during constant velocity rotation. J Neurophysiol 69, 996–999, 1993.

33. Angelaki DE, Perachio AA, Mustari MJ, Strunk CL. Role of irregular otolith afferents in the steady-state nystagmus during off-vertical axis rotation. J Neurophysiol 68, 1895–1900, 1992.

34. Angelaki DE, Shaikh AG, Green AM, Dickman JD. Neurons compute internal models of the physical laws of motion. Nature 430, 560–564, 2004.

35. Angelaki DE, Wei M, Merfeld DM. Vestibular discrimination of gravity and translational acceleration. Ann N Y Acad Sci 942, 114–127, 2001.

36. Angelaki DE, Zhou HH, Wei M. Foveal versus full-field visual stabilization strategies for translational and rotational head movements. J Neurosci 23, 1104–1108, 2003.

37. Asawavichiangianda S, Fujimoto M, Mai M, Desroches H, Rutka J. Significance of head-shaking nystagmus in the evaluation of the dizzy patient. Acta Otolaryngol Suppl 540, 27–33, 1999.

38. Ashton JC, Zheng Y, Liu P, Darlington CL, Smith PF. Immunohistochemical characterisation and localisation of cannabinoid CB1 receptor protein in the rat vestibular nucleus complex and the effects of unilateral vestibular deafferentation. Brain Res 1021, 264–271, 2004.

39. Averbuch-Heller L, Rottach KG, Zitovsky AZ, et al. Torsional eye movements in patients with skew deviation and spasmodic torticollis: responses to static and dynamic head roll. Neurology 48, 506–514, 1997.

40. Aw ST, Fetter M, Cremer PD, Karlberg M, Halmagyi GM. Individual semicircular canal function in superior and inferior vestibular neuritis. Neurology 57, 768–774, 2001.

41. Aw ST, Fetter M, Cremer PD, Karlberg M, Halmagyi GM. Individual semicircular canal function in superior and inferior vestibular neuritis. Neurology 57, 768–774, 2001.

42. Aw ST, Halmagyi GM, Black RA, et al. Head impulses reveal loss of individual semicircular canal function. J Vestib Res 9, 173–180, 1999.

43. Aw ST, Halmagyi GM, Curthoys IS, Todd MJ, Yavor RA. Unilateral vestibular deafferentation causes permanent impairment of the human vertical vestibulo-ocular reflex in the pitch plane. Exp Brain Res 102, 121–130, 1994.

44. Aw ST, Halmagyi GM, Curthoys IS, Todd MJ, Yavor RA. Unilateral vestibular deafferentation causes permanent impairment of the human vertical vestibulo-ocular reflex in the pitch plane. Exp Brain Res 102, 121–130, 1994.

45. Aw ST, Halmagyi GM, Haslwanter T, et al. Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations. II. Responses in subjects with unilateral vestibular loss and selective semicircular canal occlusion. J Neurophysiol 76, 4021–4030, 1996.

46. Aw ST, Haslwanter T, Fetter M, Dichgans J. Three-dimensional spatial characteristics of caloric nystagmus. Exp Brain Res 134, 289–294, 2000.

47. Aw ST, Haslwanter T, Fetter M, Heimberger J, Todd MJ. Contribution of the vertical semicircular canals to the caloric nystagmus. Acta Otolaryngol 118, 618–627, 1998.

48. Aw ST, Halmagyi GM, Haslwanter T, et al. Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations. I. Responses in normal subjects. J Neurophysiol 76, 4009–4020, 1996.

49. Aw ST, Todd MJ, Mcgarvie LA, Migliaccio AA, Halmagyi GM. Effects of unilateral vestibular deafferentation on the linear vestibulo-ocular reflex evoked by impulsive eccentric roll rotation. J Neurophysiol 89, 969–978, 2003.

50. Babalian AL, Vidal PP. Floccular modulation of vestibuloocular pathways and cerebellum-related plasticity: an in vitro whole brain study. J Neurophysiol 84, 2514–2528, 2000.

51. Bai R, Meng H, Sato H, et al. Properties of utricular-activated vestibular neurons that project to the contralateral vestibular nuclei in the cat. Exp Brain Res 147, 419–425, 2002.

52. Baker J, Goldberg J, Hermann G, Peterson BW. Optimal response planes and canal convergence in secondary neurons in vestibular nuclei of alert cats. Brain Res 294, 133–137, 1984.

53. Baker R, Highstein SM. Vestibular projections to medial rectus subdivision of oculomotor nucleus. J Neurophysiol 41, 1629–1646, 1978.

54. Baloh RW, Beykirch K, Honrubia V, Yee RD. Eye movements induced by linear acceleration on a parallel swing. J Neurophysiol 60, 2000–2013, 1988.

55. Baloh RW, Demer JL. Gravity and the vertical vestibulo-ocular reflex. Exp Brain Res 83, 427–433, 1991.

56. Baloh RW, Demer JL. Optokinetic-vestibular interaction in patients with increased gain of the vestibulo-ocular reflex. Exp Brain Res 97, 334–342, 1993.

57. Baloh RW, Enrietto J, Jacobson KM, Lin A. Age-related changes in vestibular function: a longitudinal study. Ann N Y Acad Sci 942, 210–219, 2001.

58. Baloh RW, Halmagyi GM. Disorders of the Vestibular System. Oxford Press, Oxford, 1996.

59. Baloh RW, Henn V, Jäger J. Habituation of the human vestibulo-ocular reflex with low-frequency harmonic acceleration. Am J Otolaryngol 3, 235–241, 1982.

60. Baloh RW, Honrubia V, Jacobson K. Benign positional vertigo: clinical and oculographic features in 240 cases. Neurology 37, 371–378, 1987.

61. Baloh RW, Honrubia V, Yee RD, Hess K. Changes in the human vestibulo-ocular reflex after loss of peripheral sensitivity. Ann Neurol 16, 222–228, 1984.
62. Baloh RW, Honrubia V, Yee RD, Langhofer L, Minser K. Recovery from unilateral vestibular lesions. In Keller EL, Zee DS (eds). Adaptive Processes in Visual and Oculomotor Systems. Pergamon Press, Oxford, 1986, pp 349–356.
63. Baloh RW, Jacobson K, Honrubia V. Horizontal semicircular canal variant of benign positional vertigo. Neurology 43, 2542–2549, 1993.
64. Baloh RW, Jacobson KM, Beykirch K, Honrubia V. Horizontal vestibulo-ocular reflex after acute peripheral lesions. Acta Otolaryngol (Stockh) Suppl 468, 323–327, 1989.
65. Baloh RW, Jacobson KM, Socotch TM. The effect of aging on visual-vestibuloocular responses. Exp Brain Res 95, 509–516, 1993.
66. Baloh RW, Yee RD, Honrubia V. Clinical abnormalities of optokinetic nystagmus. In Lennerstrand G, Zee DS, Keller EL (eds). Functional Basis of Ocular Motility Disorders. Pergamon, Oxford,1982, pp 311–320.
67. Baloh RW, Yue Q, Demer JL. The linear vestibulo-ocular reflex in normal subjects and patients with vestibular and cerebellar lesions. J Vestib Res 5, 349–361, 1995.
68. Bárány R. Physiologie und Pathologie des Bogengangsapparates biem Menschen. Deuticke, Vienna, 1907.
69. Barber HO, Stoyanoff S. Vertical nystagmus in routine caloric testing. Otolaryngol Head Neck Surg 95, 574–580, 1984.
70. Barmack NH. Central vestibular system: vestibular nuclei and posterior cerebellum. Brain Res Bull 60, 511–541, 2003.
71. Barmack NH, Shojaku H. Vestibularly-induced slow phase oscillations in climbing fiber responses of Purkinje cells in the cerebellar nodulus. Neuroscience 50, 1–5 (1992).
72. Barnes G. Adaptation in the oculomotor response to caloric irrigation and the merits of bithermal stimulation. Br J Audiol 29, 95–106, 1995.
73. Barnett-Cowan M, Dyde RT, Harris LR. Is an internal model of head orientation necessary for oculomotor control? Ann N Y Acad Sci 1039, 314–324, 2005.
74. Barr CC, Schultheis LW, Robinson DA. Voluntary, nonvisual control of the human vestibuloocular reflex. Acta Otolaryngol (Stockh) 81, 365–375, 1976.
75. Barratt HJ, Hood JD. Transfer of optokinetic activity to vestibular nystagmus. Acta Otolaryngol (Stockh) 105, 318–327, 1988.
76. Bartl K, Schneider E, Glasauer S. Dependence of the torsional vestibulo-ocular reflex on the direction of gravity. Ann N Y Acad Sci 1039, 455–458, 2005.
77. Becker W, Raab S, Jurgens R. Circular vection during voluntary suppression of optokinetic reflex. Exp Brain Res 144, 554–557, 2002.
78. Bello S, Paige GD, Highstein SM. The squirrel monkey vestibulo-ocular reflex and adaptive plasticity in yaw, pitch, and roll. Exp Brain Res 87, 57–66, 1991.
79. Belton T, McCrea RA. Context contingent signal processing in the cerebellar flocculus and ventral paraflocculus during gaze saccades. J Neurophysiol 92, 797–807, 2004.
80. Bense S, Bartenstein P, Lochmann M, et al. Metabolic changes in vestibular and visual cortices in acute vestibular neuritis. Ann Neurol 56, 624–630, 2004.
81. Bense S, Deutschlander A, Stephan T, et al. Preserved visual-vestibular interaction in patients with bilateral vestibular failure. Neurology 63, 122–128, 2004.
82. Beraneck M, Hachemaoui M, Idoux E, et al. Long-term plasticity of ipsilesional medial vestibular nucleus neurons after unilateral labyrinthectomy. J Neurophysiol 90, 184–203, 2003.
83. Beraneck M, Idoux E, Uno A, et al. Unilateral labyrinthectomy modifies the membrane properties of contralesional vestibular neurons. J Neurophysiol 92, 1668–1684, 2004.
84. Bergamin O, Straumann D. Three-dimensional binocular kinematics of torsional vestibular nystagmus during convergence on head-fixed targets in humans. J Neurophysiol 86, 113–122, 2001.
85. Bergenius J, Tribukait A, Brantberg K. The subjective horizontal at different angles of roll-tilt in patients with unilateral vestibular impairment. Brain Res Bull 40, 385–391, 1996.
86. Berthoz A. Adaptive mechanisms in eye-head coordination. In Berthoz A, Melvill Jones G (eds). Adaptive Mechanisms in Gaze Control. Elsevier, Amsterdam,1985, pp 177–201.
87. Berthoz A. The role of gaze in compensation of vestibular dysfunction: the gaze substitution hypothesis. Progr Brain Res 76, 411–420, 1988.
88. Berthoz A. How does the cerebral cortex process and utilize vestibular signals? In Baloh RW, Halmagyi GM (eds). Disorders of the Vestibular System. Oxford Press, Oxford, 1996, pp 113–125.
89. Berthoz A, Israël I, Vieville T, Zee DS. Linear head displacement measured by the otoliths can be reproduced through the saccadic system. Neurosci Lett 82, 285–290, 1987.
90. Berthoz A, Melvill Jones G. Differential visual adaptation of vertical canal-dependent vestibulo-ocular reflexes. Exp Brain Res 44, 19–26, 1981.
91. Berthoz A, Melvill Jones G. Long-term effects of dove prism vision on torsional VOR and head-eye coordination. Exp Brain Res 44, 277–283, 1981.
92. Betts GA, Barone M, Karlberg M, MacDougall H, Curthoys IS. Neck muscle vibration alters visually-perceived roll after unilateral vestibular loss. NeuroReport 11, 2659–2662, 2000.
93. Betts GA, Curthoys IS, Todd MJ. The effect of roll-tilt on ocular skew deviation. Acta Otolaryngol (Stockh) Suppl 520, 304–306, 1995.
94. Biessing R, Kommerell G. Pseudo-spontannystagmus unter der Frenzel-Brille. Laryngol Rhinol Otol (Stuttg) 67, 453–456, 1988.
95. Bisdorff AR, Wolsley CJ, Anastasopoulos D, Bronstein AM, Gresty M A. Subjective postural vertical in peripheral and central vestibular disorders. Brain 119, 1523–1534, 1996.
96. Black RA, Halmagyi GM, Thurtell MJ, Todd MJ, Curthoys IS. The active head-impulse test in unilateral peripheral vestibulopathy. Arch Neurol 62, 290–293, 2005.
96a. Blazquez PM, Hirata Y, Highstein SM. Chronic changes in inputs to dorsal Y neurons accompany VOR motor learning. J Neurophysiol published online, 2005.
97. Blazquez P, Partsalis A, Gerrits NM, Highstein SM. Input of anterior and posterior semicircular canal interneurons encoding head-velocity to the dorsal Y group of the vestibular nuclei. J Neurophysiol 83, 2891–2904, 2000.
98. Blazquez PM, Hirata Y, Heiney SA, Green AM, Highstein SM. Cerebellar signatures of vestibulo-ocular reflex motor learning. J Neurosci 23, 9742–9751, 2003.
99. Blazquez PM, Hirata Y, Highstein SM. The vestibulo-ocular reflex as a model system for motor learning: what is the role of the cerebellum? Cerebellum 3, 188–192, 2004.
100. Bles W, Bos JE, Kruit H. Motion sickness. Curr Opin Neurol 13, 19–25, 2000.
101. Bles W, de Graaf B. Ocular rotation and perception of the horizontal under static tilt conditions in patients without labyrinthine function. Acta Otolaryngol 111, 456–462, 1991.
102. Bloomberg J, Melvill Jones G, Segal B. Adaptive modification of vestibularly perceived rotation. Exp Brain Res 84, 47–56, 1991.
103. Bockisch CJ, Haslwanter T. Three-dimensional eye position during static roll and pitch in humans. Vision Res 41, 2127–2137, 2001.
104. Bockisch CJ, Straumann D, Haslwanter T. Human 3-D aVOR with and without otolith stimulation. Exp Brain Res 161, 358–367, 2005.
105. Bockisch CJ, Straumann D, Haslwanter T. Eye movements during multi-axis whole-body rotations. J Neurophysiol 89, 355–366, 2003.
106. Bockisch CJ, Straumann D, Hess K, Haslwanter T. Enhanced smooth pursuit eye movements in patients with bilateral vestibular deficits. NeuroReport 15, 2617–2620 2004.
107. Böhmer A, Baloh RW. Vertical optokinetic nystagmus and optokinetic afternystagmus in humans. J Vestib Res 1, 309–315, 1990.
108. Böhmer A, Henn V, Suzuki J-I. Vestibulo-ocular reflexes after selective plugging of the semicircular canals in the monkey—response plane determination. Brain Res 326, 291–298, 1985.
109. Böhmer A, Mast F, Jarchow T. Can a unilateral loss of otolithic function be clinically detected by assessment of the subjective visual vertical? Brain Res Bull 40, 423–429, 1996.
110. Böhmer A, Rickenmann J. The subjective visual vertical as a clinical parameter of vestibular function in peripheral vestibular diseases. J Vestib Res 5, 35–45, 1995.
111. Böhmer A, Straumann D. Pathomechanism of downbeat nystagmus: a simple hypothesis. Neurosci Lett 250, 127–130, 1998.
112. Böhmer A, Straumann D, Suzuki J-I, Hess BJM, Henn V. Contributions of single semicircular canals to caloric nystagmus as revealed by canal plugging in rhesus monkeys. Acta Otolaryngol (Stockh) 116, 513–520, 1996.
113. Boiten J, Wilmink J, Kingma H. Acute rotatory vertigo caused by a small haemorrhage of the vestibular cortex. J Neurol Neurosurg Psychiatry 74, 388, 2003.
114. Bos JE, Bles W, de Graaf B. Eye movements to yaw, pitch, and roll about vertical and horizontal axes: adaptation and motion sickness. Aviat Space Environ Med 73, 436–444, 2002.
115. Bottini G, Karnath HO, Vallar G et al. Cerebral representations for egocentric space: Functional-anatomical evidence from caloric vestibular stimulation and neck vibration. Brain 124, 1182–1196, 2001.
116. Bottini G, Paulesu E, Frith CD, Frackowiak RSJ. Functional Anatomy of the Vestibular Cortex In Collard M, Jeannerod M, Christen Y (eds). Le Cortex Vestibulaire. Editions IRVINN, Paris, 1996, pp 27–48.
117. Bottini G, Sterzi R, Paulesu E, et al. Identification of the central vestibular projections in man: a positron emission tomography activation study. Exp Brain Res 99, 164–169, 1994.
118. Boyden ES, Katoh A, Raymond JL. Cerebellum-dependent learning: the role of multiple plasticity mechanisms. Annu Rev Neurosci 27, 581–609, 2004.
119. Boyle R, Büttner U, Markert G. Vestibular nuclei activity and eye movements in the alert monkey during sinusoidal optokinetic stimulation. Exp Brain Res 57, 362–369, 1985.
120. Boyle R, Goldberg JM, Highstein SM. Inputs from regularly and irregularly discharging vestibular nerve afferents to secondary neurons in squirrel monkey vestibular nuclei. III. Correlation with vestibulospinal and vestibuloocular output pathways. J Neurophysiol 68, 471–484, 1992.
121. Brandt T, Allum JHJ, Dichgans J. Computer analysis of optokinetic nystagmus in patients with spontaneous nystagmus of peripheral vestibular origin. Acta Otolaryngol (Stockh) 57, 362–369, 1978.
122. Brandt T, Bronstein AM. Cervical vertigo. J Neurol Neurosurg Psychiatry 71, 8–12, 2001.
123. Brandt T, Deutschlander A, Glasauer S, et al. Expectation of sensory stimulation modulates brain activation during visual motion stimulation. Ann N Y Acad Sci 1039, 325–336, 2005.
124. Brandt T, Dichgans J, Büchele W. Motion habituation: inverted self-motion perception and optokinetic after-nystagmus. Exp Brain Res 21, 337–352, 1974.
125. Brandt T, Dichgans J, Koenig E. Differential effects of central versus peripheral vision on egocentric and exocentric motion perception. Exp Brain Res 16, 476–491, 1973.
126. Brandt T, Dieterich M. Skew deviation with ocular torsion: a vestibular sign of topographic diagnostic value. Ann Neurol 33, 528–534, 1993.
127. Brandt T, Dieterich M. Vestibular syndromes in the roll plane: topographic diagnosis from brain stem to cortex. Ann Neurol 36, 337–347, 1994.
128. Brandt T, Dieterich M. Why do vestibular disorders affect spatial orientation and motion perception? In Baloh RW, Halmagyi GM (eds). Disorders of the Vestibular System. Oxford Press, Oxford, 1996, pp 126–139.
129. Brandt T, Dieterich M. Vestibular syndromes in the roll plane: topographic diagnosis from brain stem to cortex. Ann Neurol 36, 337–347, 1994.
130. Brandt T, Dieterich M. Central vestibular syndromes in roll, pitch and yaw. Neuro-ophthalmol 15, 291–303, 1995.
131. Brandt T, Dieterich M. The vestibular cortex. Its locations, functions, and disorders. Ann N Y Acad Sci 871, 293–312, 1999.
132. Brandt T, Dieterich M, Strupp M. Vertigo and Dizziness: Common Complaints. Springer, London, 2005.
133. Brandt T, Glasauer S, Stephan T, et al. Visual-vestibular and visuovisual cortical interaction: new insights from fMRI and pet. Ann N Y Acad Sci 956, 230–241, 2002.

134. Brandt T, Strupp M. General vestibular testing. Clin Neurophysiol 116, 406–426, 2005.
135. Brandt TH, Botzel K, Yousry T, Dieterich M, Schulze S. Rotational vertigo in embolic stroke of the vestibular and auditory cortices. Neurology 45, 42–44, 1995.
136. Brantberg K, Fransson P-A, Magnusson M, Johansson R, Bergenius J. Short vestibulo-ocular reflex time-constant in complete unilateral vestibular lesions. Am J Otol 16, 787–792, 1995.
137. Brantberg K, Magnusson M. Asymmetric optokinetic afterresponse in patients with vestibular neuritis. J Vestib Res 1, 279–289, 1990.
138. Bremmer F. Navigation in space—the role of the macaque ventral intraparietal area (VIP). J Physiol 566, 29–35, 2005.
139. Bremmer F, Klam F, Duhamel JR, Ben HS, Graf W. Visual-vestibular interactive responses in the macaque ventral intraparietal area (VIP). Eur J Neurosci 16, 1569–1586, 2002.
140. Brettler SC, Baker JF. Timing of low frequency responses of anterior and posterior canal vestibulo-ocular neurons in alert cats. Exp Brain Res 149, 167–173, 2003.
141. Bronstein AM. Vestibular reflexes and positional manoeuvres. J Neurol Neurosurg Psychiatry 74, 289–293, 2003.
142. Bronstein AM. Vision and vertigo: some visual aspects of vestibular disorders. J Neurol 251, 381–387, 2004.
143. Bronstein AM. Vestibular reflexes and positional manoeuvres. J Neurol Neurosurg Psychiatry 74, 289–293, 2003.
144. Bronstein AM, Gresty MA. Short latency compensatory eye movement responses to transient linear head acceleration: a specific function of the otolith-ocular reflex. Exp Brain Res 71, 406–410, 1988.
145. Bronstein AM, Gresty MA. Compensatory eye movements in the presence of conflicting canal and otolith signals. Exp Brain Res 85, 697–700, 1991.
146. Bronstein AM, Gresty MA, Mossman SS. Pendular pseudonystagmus arising as a combination of head tremor and vestibular failure. Neurology 42, 1527–1531, 1992.
147. Bronstein AM, Morland AB, Ruddock KH, Gresty MA. Recovery from bilateral vestibular failure: Implications for visual and cervico-ocular function. Acta Otolaryngol (Stockh) Suppl 520, 405–407, 1995.
148. Bronstein AM, Mossman S, Luxon LM. The neck-eye reflex in patients with reduced vestibular and optokinetic function. Brain 114, 1–11, 1991.
149. Bronstein AM, Perennou DA, Guerraz M, Playford D, Rudge P. Dissociation of visual and haptic vertical in two patients with vestibular nuclear lesions. Neurology 61, 1260–1262, 2003.
150. Brookes GB, Faldon M, Kanayama R, Nakamura T, Gresty MA. Recovery from unilateral vestibular nerve section in human subjects evaluated by physiological, psychological and questionnaire assessments. Acta Otolaryngol (Stockh) Suppl 513, 40–48, 1994.
151. Brookes GB, Gresty MA, Nakamura T, Metcalfe T. Sensing and controlling rotational orientation in normal subjects and patients with loss of labyrinthine function. Am J Otol 14, 349–351, 1993.
152. Broussard DM, Kassardjian CD. Learning in a simple motor system. Learn Mem 11, 127–136, 2004.
153. Broussard DM, Priesol AJ, Tan YF. Asymmetric responses to rotation at high frequencies in central vestibular neurons of the alert cat. Brain Res 1005, 137–153, 2004.
154. Busettini C, Miles FA, Schwarz U, Carl JR. Human ocular responses to translation of the observer and of the scene: dependence on viewing distance. Exp Brain Res 100, 484–494, 1994.
155. Bush GA, Miles FA. Short-latency compensatory eye movements associated with a brief period of free fall. Exp Brain Res 108, 337–340, 1996.
156. Büttner U, Meienberg O, Schimmelpfennig B. The effect of central retinal lesions on optokinetic nystagmus in the monkey. Exp Brain Res 52, 248–256, 1983.
157. Büttner U, Henn V, Oswald HP. Vestibular related neuronal activity in the thalamus of the alert monkey during natural vestibular stimulation. Exp Brain Res 30, 435–444, 1977.
158. Büttner U, Waespe W. Vestibular nerve activity in the alert monkey during vestibular and optokinetic nystagmus. Exp Brain Res 41, 310–315, 1981.
159. Büttner-Ennever JA. Patterns of connectivity in the vestibular nuclei. Ann NY Acad Sci 656, 363–378, 1992.
160. Büttner-Ennever JA, Horn A, Schmidtke K. Cell groups of the medial longitudinal fasciculus and paramedian tracts. Rev Neurol (Paris) 145, 533–539, 1989.
161. Büttner-Ennever JA, Horn AKE. Pathways from cell groups of the paramedian tracts to the floccular region. Ann N Y Acad Sci 781, 532–540, 1996.
162. Cannon SC, Leigh RJ, Zee DS, Abel L. The effect of the rotational magnification of corrective spectacles on the quantitative evaluation of the VOR. Acta Otolaryngol (Stockh) 100, 81–88, 1985.
163. Carey JP, Della Santina CC. Principles of applied vestibular physiology. In Cummings CC (ed). Otolaryngology Head & Neck Surgery. Elsevier Mosby, Philadephia, 2005, pp 3115–3159.
164. Carey JP, Minor LB, Peng CG, et al. Changes in the three-dimensional angular vestibulo-ocular reflex following intratympanic gentamicin for Meniere's disease. J Assoc Res Otolaryngol 3, 430–443, 2002.
165. Carleton SC, Carpenter MB. Afferent and efferent connections of the medial, inferior and lateral vestibular nuclei in the cat and monkey. Brain Res 278, 29–51, 1983.
166. Carpenter M, Cowie R. Connections and oculomotor projections of the superior vestibular nucleus and cell group 'y'. Brain Res 336, 265–287, 1985.
167. Carpenter MB. Vestibular nuclei: afferent and efferent projections. Progr Brain Res 76, 5–15, 1988.
167a. Carter TL, McElligott JG. Cerebellar AMPA/KA receptor antagonism by CNQX inhibits vestibulo-ocular reflex adapation. Exp Brain Res 166, 157–169, 2005.
168. Cartwright AD, Cremer PD, Halmagyi GM, Curthoys IS. Isolated directional preponderance of caloric nystagmus: II. A neural network model. Am J Otol 21, 568–572, 2000.
169. Cartwright AD, Curthoys IS. A neural network simulation of the vestibular system: implications on the role of intervestibular nuclear coupling during vestibular compensation. Biol Cybern 75, 485–493, 1996.

170. Cartwright AD, Gilchrist DP, Burgess AM, Curthoys IS. A realistic neural-network simulation of both slow and quick phase components of the guinea pig VOR. Exp Brain Res 149, 299–311, 2003.
171. Chan WW, Galiana HL. Integrator function in the oculomotor system is dependent on sensory context. J Neurophysiol 93, 3709–3717, 2005.
172. Chen-Huang C, McCrea R, Goldberg JM. Contributions of regularly and irregularly discharging vestibular-nerve inputs to the discharge of central vestibular neurons in the alert squirrel monkey. Exp Brain Res 114, 405–422, 1997.
173. Cheng M, Outerbridge JS. Optokinetic nystagmus during selective retinal stimulation. Exp Brain Res 23, 129–139, 1975.
174. Cheung BS, Howard IP. Optokinetic torsion: dynamics and relation to circularvection. Vision Res 31, 1327–1335, 1991.
175. Cheung BS, Money KE, Howard IP. Dynamics of torsional optokinetic nystagmus under altered gravitoinertial forces. Exp Brain Res 102, 511–518, 1995.
176. Clarke AH, Schonfeld U, Helling K. Unilateral examination of utricle and saccule function. J Vestib Res 13, 215–225, 2003.
177. Clement G. A review of the effects of space flight on the asymmetry of vertical optokinetic and vestibulo-ocular reflexes. J Vestib Res 13, 255–263, 2003.
178. Clement G, Flandrin JM, Courjon JH. Comparison between habituation of the cat vestibulo-ocular reflex by velocity steps and sinusoidal vestibular stimulation in the dark. Exp Brain Res 142, 259–267, 2002.
179. Clement G, Maciel F. Adjustment of the vestibulo-ocular reflex gain as a function of perceived target distance in humans. Neurosci Lett 366, 115–119, 2004.
180. Clément G, Popov KE, Berthoz A. Effects of prolonged weightlessness on horizontal and vertical optokinetic nystagmus and optokinetic after-nystagmus in humans. Exp Brain Res 94, 456–462, 1993.
181. Clendaniel RA, Lasker DM, Minor LB. Differential adaptation of the linear and nonlinear components of the horizontal vestibuloocular reflex in squirrel monkeys. J Neurophysiol 88, 3534–3540, 2002.
182. Clendaniel RA, Lasker DM, Minor LB. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. IV. Responses after spectacle-induced adaptation. J Neurophysiol 86, 1594–1611, 2001.
183. Cohen B. Erasmus Darwin's observations on rotation and vertigo. Human Neurobiol 3, 121–128, 1984.
184. Cohen B, Helwig D, Raphan T. Baclofen and velocity storage: a model of the effects of the drug on the vestibulo-ocular reflex in the rhesus monkey. J Physiol (Lond) 393, 703–725, 1987.
185. Cohen B, Henn V, Raphan T, Dennett D. Velocity storage, nystagmus, and visual-vestibular interactions in humans. Ann N Y Acad Sci 374, 421–433, 1981.
186. Cohen B, Maruta J, Raphan T. Orientation of the eyes to gravitoinertial acceleration. Ann N Y Acad Sci 942, 241–258, 2001.
187. Cohen B, Suzuki J-I, Raphan T. Role of the otolith organs in generation of horizontal nystagmus: effect of selective labyrinthine lesions. Brain Res 276, 159–164, 1983.
188. Cohen B, Uemura T, Takemori S. Effects of labyrinthectomy on optokinetic nystagmus (OKN) and optokinetic after-nystagmus (OKAN). Int J Equilib Res 3, 88–93, 1973.
189. Cohen B, Wearne S, Dai M, Raphan T. Spatial orientation of the angular vestibulo-ocular reflex. J Vestib Res 9, 163–172, 1999.
190. Cohen H, Cohen B, Raphan T, Waespe W. Habituation and adaptation of the vestibulo-ocular reflex; a model of differential control by the vestibulo-cerebellum. Exp Brain Res 110, 110–120, 1993.
191. Cohen HS. Side-lying as an alternative to the Dix-Hallpike test of the posterior canal. Otol Neurotol 25, 130–134, 2004.
192. Colebatch JG. Vestibular evoked potentials. Curr Opin Neurol 14, 21–26, 2001.
193. Colebatch JG, Halmagyi GM. Vestibular evoked potentials in human neck muscles before and after unilateral vestibular deafferentation. Neurology 42, 1992.
194. Collewijn H. The Oculomotor System of the Rabbit and its Plasticity. Springer, New York, 1981.
195. Collewijn H, Martins AJ, Steinman RB. Compensatory eye movements during active and passive head movements: fast adaptation to changes in visual magnification. J Physiol (Lond) 340, 259–286, 1983.
196. Collewijn H, Smeets JB. Early components of the human vestibulo-ocular response to head rotation: latency and gain. J Neurophysiol 84, 376–389, 2000.
197. Collewijn H, Van der Steen J, Ferman L, Jansen TC. Human ocular counterroll: assessment of static and dynamic properties from electromagnetic scleral coil recordings. Exp Brain Res 59, 185–196, 1985.
198. Correia MJ, Kolev OI, Rupert AH, Guedry FE. Vertical optokinetic nystagmus and after-responses during backward tilt. Aviat Space Environ Med 68, 289–295, 1997.
199. Crane BT, Demer JL. A linear canal-otolith interaction model to describe the human vestibulo-ocular reflex. Biol Cybern 81, 109–118, 1999.
200. Crane BT, Demer JL. Human gaze stabilization during natural activities: translation, rotation, magnification, and target distance effects. J Neurophysiol 78, 2129–2144, 1997.
201. Crane BT, Demer JL. Human gaze stabilization during natural activities: translation, rotation, magnification, and target distance effects. J Neurophysiol 78, 2129–2144, 1997.
202. Crane BT, Demer JL. Human horizontal vestibulo-ocular reflex initiation: effects of acceleration, target distance, and unilateral deafferentation. J Neurophysiol 80, 1151–1166, 1998.
203. Crane BT, Tian J, Wiest G, Demer JL. Initiation of the human heave linear vestibulo-ocular reflex. Exp Brain Res 148, 247–255, 2003.
204. Crane BT, Tian JR, Demer JL. Human angular vestibulo-ocular reflex initiation: relationship to Listing's Law. Ann N Y Acad Sci 1039, 26–35, 2005.
205. Crane BT, Tian JR, Demer JL. Initial vestibulo-ocular reflex during transient angular and linear acceleration in human cerebellar dysfunction. Exp Brain Res 130, 486–496, 2000.
206. Crane BT, Tian JR, Ishiyama A, Demer JL. Initiation and cancellation of the human heave linear vestibulo-ocular reflex after unilateral vestibular deafferentation. Exp Brain Res. 161, 519–526, 2005.

207. Crane BT, Viirre ES, Demer JL. The human horizontal vestibulo-ocular reflex during combined linear and angular acceleration. Exp Brain Res 114, 304–320, 1997.
208. Crane BT, Viirre ES, Demer JL. The human horizontal vestibulo-ocular reflex during combined linear and angular acceleration. Exp. Brain Res. 114, 304–320, 1997.
209. Cremer PD, Halmagyi GM, Aw ST, et al. Semicircular canal plane head impulses detect absent function of individual semicircular canals. Brain 121, 699–716, 1998.
210. Cremer PD, Migliaccio AA, Halmagyi GM, Curthoys IS. Vestibulo-ocular reflex pathways in internuclear ophthalmoplegia. Ann Neurol 45, 529–533, 1999.
211. Cremer PD, Migliaccio AA, Pohl DV, et al. Posterior semicircular canal nystagmus is conjugate and its axis is parallel to that of the canal. Neurology 54, 2016–2020, 2000.
212. Cremer PD, Minor LB, Carey JP, Della Santina CC. Eye movements in patients with superior canal dehiscence syndrome align with the abnormal canal. Neurology 55, 1833–1841, 2000.
213. Cullen KE. Sensory signals during active versus passive movement. Curr Opin Neurobiol 14, 698–706, 2004.
214. Cullen KE, Chen-Huang C, McCrea R. Firing behavior of brain stem neurons during voluntary cancellation of the horizontal vestibuloocular reflex. II. Eye movement related neurons. J Neurophysiol 70, 844–856, 1993.
215. Cullen KE, Minor LB. Semicircular canal afferents similarly encode active and passive head-on-body rotations: implications for the role of vestibular efference. J Neurosci 22, RC226, 2002.
216. Cullen KE, Roy JE. Signal processing in the vestibular system during active versus passive head movements. J Neurophysiol 91, 1919–1933, 2004.
217. Curthoys IS. Generation of the quick phase of horizontal vestibular nystagmus. Exp Brain Res 143, 397–405, 2002.
218. Curthoys IS. The role of ocular torsion in visual measures of vestibular function. Brain Res Bull 40, 399–405, 1996.
219. Curthoys IS. Eye movements produced by utricular and saccular stimulation. Aviat Space Environ Med Suppl S8, A192–A197, 1987.
220. Curthoys IS, Betts GA, Burgess AM, et al. The planes of the utricular and saccular maculae of the guinea pig. Ann N Y Acad Sci 871, 27–34, 1999.
221. Curthoys IS, Dai MJ, Halmagyi GM. Human ocular torsional position before and after unilateral vestibular neurectomy. Exp Brain Res 85, 218–225, 1991.
222. Curthoys IS, Halmagyi GM. Vestibular compensation: a review of the oculomotor, neural, and clinical consequences of unilateral vestibular loss. J Vestib Res 5, 67–107, 1995.
223. Curthoys IS, Halmagyi GM. Vestibular compensation. Adv Otorhinolaryngol 55, 82–110, 1999.
224. Curthoys IS, Markham CH. Planar relationships of the semicircular canals in man. Acta Otolaryngol (Stockh) 80, 185–196, 1975.
225. Curthoys IS, Oman CM. Dimensions of the horizontal semicircular duct. ampulla and utricle in the human. Acta Otolaryngol (Stockh) 103, 254–261, 1987.
226. Dai M, Raphan T, Cohen B. Spatial orientation of the vestibular system: dependence of optokinetic after-nystagmus on gravity. J Neurophysiol 66, 1422–1439, 1991.
226a. Dai M, Raphan T, Cohen B. Effects of baclofen on the angular vestibulo-ocular reflex. Exp Brain Res published online, 2005.
227. Dai M, Raphan T, Kozlovskaya I, Cohen B. Modulation of vergence by off-vertical yaw axis rotation in the monkey: normal characteristics and effects of space flight. Exp Brain Res 111, 21–29, 1996.
228. Dai MJ, Curthoys IS, Halmagyi GM. Linear acceleration perception in the roll plane before and after unilateral vestibular neurectomy. Exp Brain Res 77, 315–328, 1989.
229. Darlington CL, Dutia MB, Smith PF. The contribution of the intrinsic excitability of vestibular nucleus neurons to recovery from vestibular damage. Eur J Neurosci 15, 1719–1727, 2002.
230. Darlington CL, Smith PF. Molecular mechanisms of recovery from vestibular damage in mammals: recent advances. Prog Neurobiol 62, 313–325, 2000.
231. Darlington CL, Smith PF. What neurotransmitters are important in the vestibular system. In Baloh RW, Halmagyi GM (eds). Disorders of the Vestibular System. Oxford, Oxford, 1996, pp 140–144.
232. Darlot C, Denise P, Droulez J, Cohen B, Berthoz A. Eye movements induced by off-vertical axis rotation (OVAR) at small angles of tilt. Exp Brain Res 73, 91–105, 1989.
233. Darlot C, Toupet M, Denise P. Unilateral vestibular neuritis with otolithic signs and off-vertical axis rotation. Acta Otolaryngol (Stockh) 117, 7–12, 1997.
234. Das VE, Dell'Osso LF, Leigh RJ. Enhancement of the vestibulo-ocular reflex by prior eye movements. J Neurophysiol 81, 2884–2892, 1999.
235. Das VE, Yaniglos S, Leigh RJ. The influence of light on modulation of the human vestibulo-ocular reflex. J Vestib Res 10, 51–55, 2000.
236. Davies R. Bedside neuro-otological examination and interpretation of commonly used investigations. J Neurol Neurosurg Psychiatry 75 Suppl 4, iv32–iv44, 2004.
237. de Graaf B, Bos JE, Groen E. Saccular impact on ocular torsion. Brain Res Bull 40, 321–330, 1996.
238. De Waele C, Baudonniere PM, Lepecq JC, Tran Ba HP, Vidal PP. Vestibular projections in the human cortex. Exp Brain Res 141, 541–551, 2001.
239. de Waele C, Mühlethaler M, Vidal P-P. Neurochemistry of the central vestibular pathways. Brain Res Bull 20, 24–46, 1995.
240. Debette S, Michelin E, Henon H, Leys D. Transient rotational vertigo as the initial symptom of a middle cerebral artery territory infarct involving the insula. Cerebrovasc. Dis. 16, 97–98, 2003.
241. Della Santina CC, Potyagaylo V, Migliaccio AA, Minor LB, Carey JP. Orientation of human semicircular canals measured by three-dimensional multiplanar CT reconstruction. J Assoc Res Otolaryngol, published online, 2005.
242. Della Santina CC, Cremer PD, Carey JP, Minor LB. Comparison of head thrust test with head autorotation test reveals that the vestibulo-ocular reflex is enhanced during voluntary head movements. Arch Otolaryngol Head Neck Surg 128, 1044–1054, 2002.

243. Della Santina CC, Cremer PD, Carey JP, Minor LB. The vestibulo-ocular reflex during self-generated head movements by human subjects with unilateral vestibular hypofunction: improved gain, latency, and alignment provide evidence for preprogramming. Ann N Y Acad Sci 942, 465–466, 2001.
243a. Demer JL, Clark RA. Magnetic resonance imaging of human extraocular muscles during static ocular counter-rolling. J Neurophysiol 94, 3292–3302, 2005.
244. Demer JL, Crane BT, Tian JR. Human angular vestibulo-ocular reflex axis disconjugacy: relationship to magnetic resonance imaging evidence of globe translation. Ann N Y Acad Sci 1039, 15–25, 2005.
245. Demer JL, Porter FI, Goldberg J, Jenkins JA, Schmidt K. Adaptation to telescopic spectacles: vestibulo-ocular reflex plasticity. Invest Ophthalmol Vis Sci 30, 159–170, 1989.
246. Demer JL, Robinson DA. Effects of reversible lesions and stimulation of olivocerebellar system on vestibuloocular reflex plasticity. J Neurophysiol 47, 1084–1107, 1982.
247. Demer JL, Zee DS. Vestibulo-ocular and optokinetic deficits in albinos with congenital nystagmus. Invest Ophthalmol Vis Sci 25, 74–78, 1984.
248. Deutschlander A, Bense S, Stephan T, et al. Sensory system interactions during simultaneous vestibular and visual stimulation in PET. Hum Brain Mapp 16, 92–103, 2002.
249. Deutschlander A, Bense S, Stephan T, et al. Rollvection versus linearvection: comparison of brain activations in PET. Hum Brain Mapp 21, 143–153, 2004.
250. Diamond SG, Markham CH. Ocular counterrolling as an indicator of vestibular otolith function. Neurology 33, 1460–1469, 1983.
251. Dickman JD, Angelaki DE. Dynamics of vestibular neurons during rotational motion in alert rhesus monkeys. Exp Brain Res 155, 91–101, 2004.
252. Dickman JD, Fang Q. Differential central projections of vestibular afferents in pigeons. J Comp Neurol 367, 110–131, 1996.
253. Dieterich M. The topographic diagnosis of acquired nystagmus in brainstem disorders. Strabismus 10, 137–145, 2002.
254. Dieterich M. Dizziness. Neurologist 10, 154–164, 2004.
255. Dieterich M, Bartenstein P, Spiegel S, et al. Thalamic infarctions cause side-specific suppression of vestibular cortex activations. Brain 128, 2052–2067, 2005.
256. Dieterich M, Bense S, Lutz S, et al. Dominance for vestibular cortical function in the non-dominant hemisphere. Cereb Cortex 13, 994–1007, 2003.
257. Dieterich M, Bense S, Stephan T, et al. Medial vestibular nucleus lesions in Wallenberg's syndrome cause decreased activity of the contralateral vestibular cortex. Ann N Y Acad Sci 1039, 368–383, 2005.
258. Dieterich M, Bense S, Stephan T, Yousry TA, Brandt T. fMRI signal increases and decreases in cortical areas during small-field optokinetic stimulation and central fixation. Exp Brain Res 148, 117–127, 2003.
259. Dieterich M, Brandt T. Ocular torsion and tilt of subjective visual vertical are sensitive brainstem signs. Ann Neurol 33, 292–299, 1993.
260. Dieterich M, Brandt T. Wallenberg's syndrome: lateropulsion, cyclorotation, and subjective visual vertical in thirty-six patients. Ann Neurol 31, 399–408, 1992.
261. Dieterich M, Brandt T. Thalamic infarctions: differential effects on vestibular function in the roll plane (35 patients). Neurology 43, 1732–1740, 1993.
262. Dieterich M, Brandt T. Vestibular system: anatomy and functional magnetic resonance imaging. Neuroimaging Clin N Am 11, 263–273, 2001.
263. Dieterich M, Zink R, Weiss A, Brandt T. Galvanic stimulation in bilateral vestibular failure: 3-D ocular motor effects. NeuroReport 10, 3283–3287, 1999.
264. du Lac S. Candidate cellular mechanisms of vestibulo-ocular reflex plasticity. Ann N Y Acad Sci 781, 489–498, 1996.
265. Dumas G, Lavieille JP, Schmerber S. Vibratory test and head shaking test and caloric test: a series of 87 patients. Ann Otolaryngol Chir Cervicofac 121, 22–32, 2004.
266. Eggers SD, De Pennington N, Walker MF, Shelhamer M, Zee DS. Short-term adaptation of the VOR: non-retinal-slip error signals and saccade substitution. Ann N Y Acad Sci 1004, 94–110, 2003.
267. Eggers SD, Zee DS. Central vestibular disorders. In Cummings CC (ed). Otolaryngology Head & Neck Surgery. Elsevier Mosby, Philadelphia, 2005, pp 3254–3290.
268. Eggers SD, Zee DS. Evaluating the dizzy patient: bedside examination and laboratory assessment of the vestibular system. Semin Neurol 23, 47–58, 2003.
268a. Eickhoff SB, Weiss PH, Amunts K, Fink GR, Zilles K. Identifying human parieto-insular vestibular cortex using fMRI and cytoarchitectonic mapping. Hum Brain Mapp, Published online, 2005.
269. Emri M, et al. Cortical projection of peripheral vestibular signaling. J Neurophysiol 89, 2639–2646, 2003.
270. Estanol B, Romero R, De Viteri MS, Mateos JH, Corvera J. Oculomotor and oculovestibular function in a hemispherectomy patient. Arch Neurol 37, 365–368, 1980.
271. Ewald JR. Physiologishe Untersuchungen über das Endorgan des Nervus Octavus. Bergmann, Wiesbaden, 1892.
272. Farooq SJ, Proudlock FA, Gottlob I. Torsional optokinetic nystagmus: normal response characteristics. Br J Ophthalmol 88, 796–802, 2004.
273. Farrow K, Broussard DM. Commissural inputs to secondary vestibular neurons in alert cats after canal plugs. J Neurophysiol 89, 3351–3353, 2003.
274. Fasold O, von Brevern M, Kuhberg M, et al. Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. Neuroimage 17, 1384–1393, 2002.
275. Feil R, Hartmann J, Luo C, et al. Impairment of LTD and cerebellar learning by Purkinje cell-specific ablation of cGMP-dependent protein kinase I. J Cell Biol 163, 295–302, 2003.
276. Fernandez C, Goldberg J. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. II. Response to sinusoidal stimulation and dynamics of peripheral vestibular system. J Neurophysiol 34, 661–675, 1971.
277. Fetter M. Assessing vestibular function: which tests, when? J Neurol 247, 335–342, 2000.

278. Fetter M, Dichgans J. Vestibular neuritis spares the inferior division of the vestibular nerve. Brain 119, 755–763, 1996.
279. Fetter M, Dichgans J. Adaptive mechanisms of vor compensation after unilateral peripheral vestibular lesions in humans. J Vestib Res 1, 9–22, 1990.
280. Fetter M, Hain TC, Zee DS. Influence of eye and head position on the vestibulo-ocular reflex. Exp Brain Res 64, 208–216, 1986.
281. Fetter M, Misslisch, H, Sievering D, Tweed D. Effects of full-field visual input on the three-dimensional properties of the human vestibuloocular reflex. J Vestib Res 5, 201–209, 1995.
282. Fetter M, Tweed D, Hermann W, Wohland-Braun B, Koenig E. The influence of head position and head reorientation on the axis of eye rotation and the vestibular time constant during postrotatory nystagmus. Exp Brain Res 91, 121–128, 1992.
283. Fetter M, Heimberger J, Black R, Hermann W, Sievering F, Dichgans J. Otolith semicircular canal interaction during postrotatory nystagmus in humans. Exp Brain Res 108, 463–472, 1996.
284. Fetter M, Zee DS. Recovery from unilateral labyrinthectomy in rhesus monkey. J. Neurophysiol 59, 370–393, 1988.
285. Fetter M, Zee DS, Koenig E, Dichgans J. Head-shaking nystagmus during vestibular compensation in humans and rhesus monkeys. Acta Otolaryngol (Stockh) 110, 175–181, 1990.
286. Fetter M, Zee DS, Proctor LR. Effect of lack of vision and of occipital lobectomy upon recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 59, 394–407, 1988.
287. Fife TD, Baloh RW, Duckwiler GR. Isolated dizziness in vertebrobasilar insufficiency. clinical features, angiography, and follow-up. J Stroke Cerebrovasc Dis 4, 4–12, 1994.
288. Fletcher WA, Hain TC, Zee DS. Optokinetic nystagmus and after-nystagmus in human beings: relationship to nonlinear processing of information about retinal slip. Exp Brain Res 81, 46–52, 1990.
289. Flourens, P. Recherches Experimentales sur les Proprietes et les Fonetions du Systeme Nerveux dans Ies Animaux Vertebres. Crevot, Paris, 1824.
290. Fluur E. Interaction between the utricles and the horizontal semicircular canals. Acta Otolaryngol (Stockh) 76, 349–352, 1973.
291. Formby C, Robinson DA. Measurement of vestibular ocular reflex (VOR) time constants with a caloric step stimulus. J Vestib Res 10, 25–39, 2000.
292. Foster CA, Demer JL, Morrow MJ, Baloh RW. Deficits of gaze stability in multiple axes following unilateral vestibular lesions. Exp Brain Res 116, 501–509, 1997.
293. Francis DA, Bronstein AM, Rudge P, du Boulay EP. The site of brainstem lesions causing semicircular canal paresis: an MRI study. J Neurol Neurosurg Psychiatry 55, 446–449, 1992.
294. Friberg L, Olsen T, Roland P, Paulson O, Lassen N. Focal increase of blood flow in the cerebral cortex of man during vestibular stimulation. Brain 108, 609–623, 1985.
295. Fujimoto C, Iwasaki S, Matsuzaki M, Murofushi T. Lesion site in idiopathic bilateral vestibulopathy: a galvanic vestibular-evoked myogenic potential study. Acta Otolaryngol 125, 430–432, 2005.
296. Fukushima K. Corticovestibular interactions: anatomy, electrophysiology, and functional considerations. Exp Brain Res 117, 1–16, 1997.
297. Fukushima K. The interstitial nucleus of Cajal in the midbrain reticular formation and vertical eye movement. Neurosci Res 10, 159–187, 1991.
298. Fukushima K, Fukushima J, Chin S, Tsunekawa H, Kaneko CRS. Cross axis vestibulo-ocular reflex induced by pursuit training in alert monkeys. Neurosci Res 25, 255–265, 1996.
299. Fukushima K, Fukushima J, Ohashi T, Kase M. Possible downward burster-driving neurons related to the anterior semicircular canal in the region of the interstitial nucleus of Cajal in alert cats. Neurosci Res 12, 536–544, 1991.
300. Fukushima K, Fukushima J, Yamanobe T, Shinmei Y, Kurkin S. Adaptive eye movements induced by cross-axis pursuit—vestibular interactions in trained monkeys. Acta Otolaryngol Suppl 545, 73–79, 2001.
301. Furman JM, Balaban CD, Pollack IF. Vestibular compensation in a patient with a cerebellar infarction. Neurology 48, 916–920, 1997.
302. Furman JM, Cass SP. Laboratory evaluation 1. Electro nystagmography and rotational testing. In Baloh RW, Halmagyi GM (eds). Disorders of the Vestibular System. Oxford, Oxford, 1996, pp 191–210.
303. Furman JM, Muller ML, Redfern MS, Jennings JR. Visual-vestibular stimulation interferes with information processing in young and older humans. Exp Brain Res 152, 383–392, 2003.
304. Furman JM, Redfern MS. Effect of aging on the otolith-ocular reflex. J Vestib Res 11, 91–103, 2001.
305. Furman JM, Redfern MS. Visual-vestibular interaction during OVAR in the elderly. J Vestib Res 11, 365–370, 2001.
306. Furman JM, Schor RH. Semicircular canal-otolith organ interaction during off-vertical axis rotation in humans. J Assoc Res Otolaryngol 2, 22–30, 2001.
307. Furman JM, Whitney SL. Central causes of dizziness. Phys Ther 80, 179–187, 2000.
308. Furman JMR, Crumrime PK, Reinmuth OM. Epileptic nystagmus. Ann Neurol 27, 686–688, 1990.
309. Furman JMR, Hain TC, Paige GD. Central adaptation models of the vestibuloocular and optokinetic systems. Biol Cybern 61, 255–264, 1989.
310. Furman JMR, Schor RH, Kamerer DB. Off-vertical axis rotational responses in patients with unilateral peripheral vestibular lesions. Ann Otol Rhinol Laryngol 102, 137–143, 1993.
311. Fushiki H, Takata S, Yasuda K, Watanabe Y. Directional preponderance in pitch circular vection. J Vestib Res 10, 93–98, 2000.
312. Galetta SL, Liu GT, Raps EC, Solomon D, Volpe NJ. Cyclodeviation in skew deviation. Am J Ophthalmol 118, 509–514, 1994.
313. Galiana HL. A nystagmus strategy to linearize the vestibulo-ocular reflex. IEEE Trans Biomed Engineering 38, 532–543, 1991.
314. Galiana HL, Smith HL, Katsarkas A. Comparison of linear vs. non-linear methods for analyzing the vestibulo-ocular reflex (VOR). Acta Otolaryngol (Stockh) 115, 585–596, 1995.
315. Galiana HL, Smith HL, Katsarkas A. Modelling nonlinearities in the vestibulo-ocular reflex (VOR) after unilateral or bilateral loss of peripheral vestibular function. Exp Brain Res 137, 369–386, 2001.

316. Galimberti CA, Versino M, Sertori I, et al. Epileptic skew deviation. Neurology 50, 1469–1472, 1998.
317. Garbutt S, Han Y, Kumar AN, et al. Vertical optokinetic nystagmus and saccades in normal human subjects. Invest Ophthalmol Vis Sci 44, 3833–3841, 2003.
318. Garbutt S, Han Y, Kumar AN, et al. Disorders of vertical optokinetic nystagmus in patients with ocular misalignment. Vision Res 43, 347–357, 2003.
319. Garbutt S, Harris CM. Abnormal vertical optokinetic nystagmus in infants and children. Br J Ophthalmol 84, 451–455, 2000.
320. Garbutt S, Thakore N, Rucker J, et al. Effects of visual fixation and convergence on periodic alternating nystagmus due to MS. Neuro-ophthalmology 28, 221–229, 2004.
321. Gdowski GT, Belton T, McCrea RA. The neurophysiological substrate for the cervico-ocular reflex in the squirrel monkey. Exp Brain Res 140, 253–264, 2001.
322. Gdowski GT, McCrea RA. Neck proprioceptive inputs to primate vestibular nucleus neurons. Exp Brain Res 135, 511–526, 2000.
323. Gellman RS, Carl JR, Miles FA. Short latency ocular-following responses in man. Vis Neurosci 5, 107–122, 1990.
324. Gianna CC, Gresty MA, Bronstein AM. The human linear vestibulo-ocular reflex to transient accelerations: visual modulation of suppression and enhancement. J Vestib Res 10, 227–238, 2000.
325. Gianna-Poulin CC, Stallings V, Black FO. Eye movement responses to active, high-frequency pitch and yaw head rotations in subjects with unilateral vestibular loss or posterior semicircular canal occlusion. J Vestib Res 13, 131–141, 2003.
326. Gilchrist DP, Cartwright AD, Burgess AM, Curthoys IS. Behavioural characteristics of the quick phase of vestibular nystagmus before and after unilateral labyrinthectomy in guinea pig. Exp Brain Res 149, 289–298, 2003.
327. Gizzi M, Raphan T, Rudolph S, Cohen B. Orientation of human optokinetic nystagmus to gravity: a model-based approach. Exp Brain Res 99, 347–360, 1994.
328. Glasauer S, von LH, Siebold C, Buttner U. Vertical vestibular responses to head impulses are symmetric in downbeat nystagmus. Neurology 63, 621–625, 2004.
329. Gliddon CM, Darlington CL, Smith PF. GABAergic systems in the vestibular nucleus and their contribution to vestibular compensation. Prog Neurobiol 75, 53–81, 2005.
330. Godfrey DA, Xu J, Godfrey MA, Li H, Rubin AM. Effects of unilateral vestibular ganglionectomy on glutaminase activity in the vestibular nerve root and vestibular nuclear complex of the rat. J Neurosci Res 77, 603–612, 2004.
331. Goldberg JM. Afferent diversity and the organization of central vestibular pathways. Exp. Brain Res 130, 277–297, 2000.
332. Goldberg JM, Fernandez C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. 1. Resting discharge and response to constant angular accelerations. J Neurophysiol 34, 635–660, 1971.
333. Goldberg JM, Lysakowski A, Fernández C. Structure and function of vestibular nerve fibers in the chinchilla and squirrel monkey. Ann N Y Acad Sci 656, 92–107, 1992.
334. Goltz HC, Irving EL, Steinbach M, Eizenman M. Vertical eye position control in darkness: orbital position and body orientation interact to modulate drift velocity. Vision Res 37, 789–798, 1997.
335. Gonshor A, Melvill Jones G. Extreme vestibuloocular adaptation induced by prolonged optical reversal of vision. J Physiol (Lond) 256, 381–414, 1976.
336. Gonshor A, Melvill Jones G. Short-term adaptive changes in the human vestibulo-ocular reflex. J Physiol (Lond) 256, 361–379, 1976.
337. Goto F, Meng H, Bai R, et al. Eye movements evoked by the selective stimulation of the utricular nerve in cats. Auris Nasus Larynx 30, 341–348, 2003.
338. Goto F, Meng H, Bai R, et al. Eye movements evoked by selective saccular nerve stimulation in cats. Auris Nasus Larynx 31, 220–225, 2004.
339. Grad A, Baloh RW. Vertigo of vascular origin. Clinical and electronystagmographic features in 84 cases. Arch Neurol 46, 281–284, 1989.
340. Graf W, Ezure K. Morphology of vertical canal related second order vestibular neurons in the cat. Exp Brain Res 63, 35–48, 1986.
341. Graham BP, Dutia MB. Cellular basis of vestibular compensation: analysis and modelling of the role of the commissural inhibitory system. Exp Brain Res 137, 387–396, 2001.
342. Grassi S, Pettorossi VE. Synaptic plasticity in the medial vestibular nuclei: role of glutamate receptors and retrograde messengers in rat brainstem slices. Prog Neurobiol 64, 527–553, 2001.
343. Green A, Galiana HL. Exploring sites for short-term VOR modulation using a bilateral model. Ann N Y Acad Sci 781, 625–628, 1996.
344. Green AM, Angelaki DE. Resolution of sensory ambiguities for gaze stabilization requires a second neural integrator. J Neurosci 23, 9265–9275, 2003.
345. Green AM, Angelaki DE. An integrative neural network for detecting inertial motion and head orientation. J Neurophysiol 92, 905–925, 2004.
346. Green AM, Galiana HL. Hypothesis for shared central processing of canal and otolith signals. J Neurophysiol 80, 2222–2228, 1998.
347. Gresty M, Barratt H, Bronstein A, Page NG. Clinical aspects of otolith-oculomotor relationships. In Keller EL, Zee DS (eds). Adaptive Processes in Visual and Oculomotor Systems. Pergamon Press, 1986, pp 357–365.
348. Gresty MA. Vestibular tests in evolution. 1. Otolith testing. In Baloh RW, Halmagyi GM (eds). Disorders of the Vestibular System. Oxford, New York,1997, pp 243–255.
349. Gresty MA, Barratt HJ, Page NG, Ell JJ. Assessment of vestibulo-ocular reflexes in congenital nystagmus. Ann Neurol 17, 129–136, 1985.
350. Gresty MA, Bronstein AM. Testing otolith function. Br J Audiol 26, 125–136, 1992.
351. Gresty MA, Bronstein AM, Barratt H. Eye movement responses to combined linear and angular head movement. Exp Brain Res 65, 377–384, 1987.
352. Gresty MA, Bronstein AM, Brandt T, Dieterich M. Neurology of otolith function: peripheral and central disorders. Brain 115, 647–673, 1992.
353. Gresty MA, Hess K, Leech J. Disorders of the vestibuloocular reflex producing oscillopsia and

mechanisms compensating for loss of labyrinthine function. Brain 100, 693–716 1977.
354. Gresty MA, Lempert T. Pathophysiology and clinical testing of otolith dysfunction. Adv Otorhinolaryngol 58, 15–33, 2001.
355. Groen E, Bos JE, de Graaf B. Contribution of the otoliths to the human torsional vestibulo-ocular reflex. J Vestib Res 9, 27–36, 1999.
356. Groen E, de Graaf B, Bles W, Bos JE. Ocular torsion before and after 1 hour centrifugation. Brain Res Bull 40, 331–335, 1996.
357. Grossman GE, Leigh RJ, Abel LA, Lanska DJ, Thurston SE. Frequency and velocity of rotational head perturbations during locomotion. Exp Brain Res 70, 470–476, 1988.
358. Grunfeld EA, Morland AB, Bronstein AM, Gresty MA. Adaptation to oscillopsia: a psychophysical and questionnaire investigation. Brain 123, 277–290, 2000.
359. Grüsser O-J. Purkyne's contribution to the physiology of the visual, the vestibular and the oculomotor systems. Human Neurobiol 3, 129–144, 1984.
360. Guldin WO, Grusser OJ. Is there a vestibular cortex? Trends Neurosci 21, 254–259, 1998.
360a. Guilding C, Dutia MB. Early and late changes in vestibular neuronal excitability after deafferentation. Neuroreport 16, 1415–1418, 2005.
361. Haddad GM, Friendlich AR, Robinson DA. Compensation of nystagmus after VIIIth nerve lesions in vestibulo-cerebellectomized cats. Brain Res 135, 192–196 1977.
362. Hafstrom A, Fransson PA, Karlberg M, Magnusson M. Idiosyncratic compensation of the subjective visual horizontal and vertical in 60 patients after unilateral vestibular deafferentation. Acta Otolaryngol 124, 165–171, 2004.
363. Hain TC, Buettner UW. Static roll and the vestibulo-ocular reflex (VOR). Exp Brain Res 83, 463–471, 1990.
364. Hain TC, Fetter M, Zee DS. Head-shaking nystagmus in patients with unilateral peripheral vestibular lesions. Am J Otolaryngol 8, 36–47, 1987.
365. Hain TC, Heroman SJ, Holliday M, et al. Localizing value of optokinetic afternystagmus. Ann Otol Rhinol Laryngol 103, 806–811, 1994.
366. Hain TC, Spindler J. Head-sharing nystagmus. In Sharpe JA, Barber HO (eds). The Vestibulo-Ocular Reflex and Vertigo. Raven Press, New York,1993, pp 217–228.
367. Hain TC, Zee DS. Velocity storage in labyrinthine disorders. Ann N Y Acad Sci 656, 297–304, 1992.
368. Hain TC, Zee DS. Abolition of optokinetic afternystagmus by aminoglycoside ototoxicity. Ann Otol Rhinol Laryngol 100, 580–583, 1991.
369. Hain TC, Zee DS, Maria B. Tilt-suppression of the vestibulo-ocular reflex in patients with cerebellar lesions. Acta Otolaryngol (Stockh) 105, 13–20, 1988.
370. Halmagyi GM. New clinical tests of unilateral vestibular dysfunction. J Laryngol Otol 118, 589–600, 2004.
371. Halmagyi GM, Aw ST, Cremer PD, Curthoys IS, Todd MJ. Impulsive testing of individual semicircular canal function. Ann N Y Acad Sci 942, 192–200, 2001.
372. Halmagyi GM, Aw ST, Karlberg M, Curthoys IS, Todd M. J. Inferior vestibular neuritis. Ann N Y Acad Sci 956, 306–313, 2002.
373. Halmagyi GM, Cremer PD, Anderson J, Murofushi T, Curthoys IS. Isolated directional preponderance of caloric nystagmus: I. Clinical significance. Am J Otol 21, 559–567, 2000.
374. Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. Arch Neurol 45, 737–739, 1988.
375. Halmagyi GM, Curthoys IS, Colebatch JG, Aw ST. Vestibular responses to sound. Ann N Y Acad Sci 1039, 54–67, 2005.
376. Halmagyi GM, Gresty MA, Gibson WPR. Ocular tilt reaction with peripheral vestibular lesion. Ann Neurol 6, 80–83, 1979.
377. Halmagyi GM, Henderson CJ. Visual symptoms of vestibular disease. Aust N Zealand J Ophthalmol 16, 177–179, 1988.
378. Halmagyi GM, Mcgarvie LA, Aw ST, Yavor RA, Todd MJ. The click-evoked vestibulo-ocular reflex in superior semicircular canal dehiscence. Neurology 60, 1172–1175, 2003.
379. Halmagyi GM, Yavor RA, Colebatch JG. Tapping the head activates the vestibular system: a new use for the clinical reflex hammer. Neurology 45, 1927–1929, 1995.
380. Hamann KF, Schuster EM. Vibration-induced nystagmus—A sign of unilateral vestibular deficit. ORL J Otorhinolaryngol Relat Spec 61, 74–79, 1999.
381. Han YH, Kumar AN, Reschke AF, et al. Vestibular and non-vestibular contributions to eye movements that compensate for head rotations during viewing of near targets. Exp Brain Res 165, 294–304, 2005.
382. Hansel C, Linden DJ, D'Angelo E. Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. Nat Neurosci 4, 467–475, 2001.
383. Haque A, Angelaki DE, Dickman JD. Spatial tuning and dynamics of vestibular semicircular canal afferents in rhesus monkeys. Exp Brain Res 155, 81–90, 2004.
384. Harris L, Beykirch K, Fetter M. The visual consequences of deviations in the orientation of the axis of rotation of the human vestibulo-ocular reflex. Vision Res 41, 3271–3281, 2001.
385. Haslwanter T, Curthoys IS, Black RA, Topple AN, Halmagyi GM. The three-dimensional human vestibulo-ocular reflex: response to long-duration yaw angular accelerations. Exp Brain Res 109, 303–311, 1996.
386. Haslwanter T, Jaeger R, Mayr S, Fetter M. Three-dimensional eye-movement responses to off-vertical axis rotations in humans. Exp Brain Res 134, 96–106, 2000.
387. Haslwanter T, Minor LB. Nystagmus induced by circular head shaking in normal human subjects. Exp Brain Res 124, 25–32, 1999.
388. Hawkins JE, Schacht J. Sketches of otohistory. Audiol Neurootol 10, 185–190, 2005.
389. Hawrylyshyn PA, Rubin PA, Tasker RR, Organ LW, Fredrickson JM. Vestibulothalamic projections in man—a sixth primary sensory pathway. J Neurophysiol 41, 394–401, 1978.
390. Hegemann S, Fitzek S, Fitzek C, Fetter M. Cortical vestibular representation in the superior temporal gyrus. J Vestib Res 14, 33–35, 2004.

391. Hegemann S, Shelhamer M, Kramer PD, Zee DS. Adaptation of the phase of the human linear vestibulo-ocular reflex (LVOR) and effects on the oculomotor neural integrator. J. Vestib Res 10, 239–247, 2000.
392. Heide W, Blossfeldt TP, Koenig E, Dichgans J. Optokinetic nystagmus, self-motion sensation and their aftereffects in patients with long-lasting peripheral visual field defects. Clin Vision Sci 5, 133–143, 1990.
393. Heimbrand S, Bronstein AM, Gresty MA, Faldon ME. Optically induced plasticity of the cervicoocular reflex in patients with bilateral absence of vestibular function. Exp Brain Res 112, 372–380, 1996.
394. Henn V. Mach on the analysis of motion sensation. Human Neurobiol 3, 145–148, 1984.
395. Henn V, Young LR, Finley C. Vestibular nucleus units in alert monkeys are also influenced by moving visual fields. Brain Res 71, 144–149, 1974.
396. Herdman SJ, Schubert MC, Das VE, Tusa RJ. Recovery of dynamic visual acuity in unilateral vestibular hypofunction. Arch Otolaryngol Head Neck Surg 129, 819–824, 2003.
397. Hess BJ, Jaggi-Schwarz K, Misslisch H. Canal-otolith interactions after off-vertical axis rotations. II. Spatiotemporal properties of roll and pitch postrotatory vestibuloocular reflexes. J Neurophysiol 93, 1633–1646, 2005.
398. Hess BJ, Lysakowski A, Minor LB, Angelaki DE. Central versus peripheral origin of vestibuloocular reflex recovery following semicircular canal plugging in rhesus monkeys. J Neurophysiol 84, 3078–3082, 2000.
399. Hess K, Dürsteler M, Reisine H. Analysis of slow phase eye velocity during the course of an acute vestibulopathy. Acta Otolaryngol (Stockh) Suppl 406, 227–230, 1984.
399a. Highstein SM, Holstein GR. The anatomy of the vestibular nuclei. Prog Brain Res 151, 157–203, 2005.
400. Highstein SM, Baker R. Excitatory termination of abducens internuclear neurons on medial rectus motoneurons: relationship to syndrome of internuclear ophthalmoplegia. J Neurophysiol 41, 1647–1661, 1987.
401. Highstein SM, Blazquez PM, Hirata Y. Responses of floccular purkinje cells following chronic adaptation of the vertical VOR [abstract]. Soc Neurosci Abstr 27, 2001.
402. Highstein SM, Partsalis A, Arikan R. Role of the Y-group of the vestibular nuclei and flocculus of the cerebellum in motor learning of the vertical vestibulo-ocular reflex. Progr Brain Res 114, 383–397, 1997.
403. Highstein SM, Rabbitt RD, Holstein GR, Boyle RD. Determinants of spatial and temporal coding by semicircular canal afferents. J Neurophysiol 93, 2359–2370, 2005.
404. Himi T, Igarashi M, Takeda N. Effect of vestibulocerebellar lesions on asymmetry of vertical optokinetic functions in the squirrel monkey. Acta Otolaryngol (Stockh) 109, 188–194 1990.
405. Hine T. Effects of asymmetric vergence on compensatory eye movements during active head rotation. J Vestib Res 1, 357–371, 1991.
406. Hirata Y, Highstein SM. Acute adaptation of the vestibuloocular reflex: signal processing by floccular and ventral parafloccular Purkinje cells. J Neurophysiol 85, 2267–2288, 2001.
407. Hirata Y, Highstein SM. Plasticity of the vertical VOR: a system identification approach to localizing the adaptive sites. Ann N Y Acad Sci 978, 480–495, 2002.
408. Hirata Y, Lockard JM, Highstein SM. Capacity of vertical VOR adaptation in squirrel monkey. J Neurophysiol 88, 3194–3207, 2002.
409. Hirvonen TP, Aalto H, Pyykkö I, Juhola, M. Phase difference of vestibulo-ocular reflex in head autorotation test. Acta Otolaryngol (Stockh) Suppl 529, 98–100, 1997.
410. Holstein GR, Martinelli GP, Cohen B. The ultrastructure of GABA-immunoreactive vestibular commissural neurons related to velocity storage in the monkey. Neuroscience 93, 171–181, 1999.
411. Holstein GR, Martinelli GP, Cohen B. Ultrastructural features of non-commissural GABAergic neurons in the medial vestibular nucleus of the monkey. Neuroscience 93, 183–193, 1999.
412. Holstein GR, Martinelli GP, Wearne S, Cohen B. Ultrastructure of vestibular commissural neurons related to velocity storage in the monkey. Neuroscience 93, 155–170, 1999.
413. Holstein GR, Rabbitt RD, Martinelli GP, et al. Convergence of excitatory and inhibitory hair cell transmitters shapes vestibular afferent responses. Proc Natl Acad Sci U S A 101, 15766–15771, 2004.
414. Horii A, Kitahara T, Smith PF, et al. Effects of unilateral labyrinthectomy on GAD, GAT1 and GABA receptor gene expression in the rat vestibular nucleus. NeuroReport 14, 2359–2363, 2003.
415. Horii A, Masumura C, Smith PF, et al. Microarray analysis of gene expression in the rat vestibular nucleus complex following unilateral vestibular deafferentation. J Neurochem 91, 975–982, 2004.
416. Howard IP, Simpson WA. Human optokinetic nystagmus is linked to the stereoscopic system. Exp Brain Res 78, 309–314, 1989.
417. Howard IP, Sun L, Shen X. Cycloversion and cyclovergence: the effects of the area and the position of the visual display. Exp Brain Res 100, 509–514, 1994.
418. Hullar TE, Della Santina CC, Hirvonen T, et al. Responses of irregularly discharging chinchilla semicircular canal vestibular-nerve afferents during high-frequency head rotations. J Neurophysiol 93, 2777–2786, 2005.
419. Hullar TE, Minor LB. High-frequency dynamics of regularly discharging canal afferents provide a linear signal for angular vestibuloocular reflexes. J Neurophysiol, 82, 2000–2005, 1999.
420. Hullar TE, Minor LB, Zee DS. Evaluation of the patient with dizziness. In Cummings CC (ed). Otolaryngology Head & Neck Surgery. Elsevier Mosby, Philadelphia, 2005, pp 3160–3199.
421. Huterer M, Cullen KE. Vestibuloocular reflex dynamics during high-frequency and high-acceleration rotations of the head on body in rhesus monkey. J Neurophysiol 88, 13–28, 2002.
422. Huygen PLM, Nicolasen MGM, Verhagen WIM, Theunissen EJJM. Contralateral hyperactive caloric

responses in unilateral labyrinthine weakness. Acta Otolaryngol (Stockh) 107, 1–4, 1989.
423. Huygen PLM, Verhagen WIM, Nicolasen MGM. Cervico-ocular reflex enhancement in labyrinthine-defective and normal subjects. Exp Brain Res 87, 457–464, 1991.
424. Ibbotson MR, Price NS, Das VE, Hietanen MA, Mustari MJ. Torsional eye movements during psychophysical testing with rotating patterns. Exp Brain Res 160, 264–267, 2005.
425. Indovina I, Maffei V, Bosco G, et al. Representation of visual gravitational motion in the human vestibular cortex. Science 308, 416–419, 2005.
426. Israël I, Bronstein AM, Kanayama R, Faldon M, Gresty MA. Visual and vestibular factors influencing vestibular "navigation". Exp Brain Res 112, 411–419, 1996.
427. Israël I, Fetter M, Koenig E. Vestibular perception of passive whole-body rotation about horizontal and vertical axes in humans: goal-directed vestibulo-ocular reflex and vestibular memory-contingent saccades. Exp Brain Res 96, 335–346, 1993.
428. Israël I, Rivaud S, Gaymard B, Berthoz A, Pierrot-Deseilligny C. Cortical control of vestibular-guided saccades. Brain 118, 1169–1184, 1995.
429. Istl-Lenz Y, Hydén D, Schwartz DWF. Response of the human vestibulo-ocular response following long-term 2x magnified visual input. Exp Brain Res 57, 448–455, 1985.
430. Ito M. Cerebellar flocculus hypothesis. Nature 363, 24–25, 1993.
431. Ito M. Long-term depression. Annu Rev Neurosci 12, 85–102, 1989.
432. Ito M. Historical review of the significance of the cerebellum and the role of Purkinje cells in motor learning. Ann N Y Acad Sci 978, 273–288, 2002.
433. Ito M, Nisimaru N, Yamamoto M. Pathways for the vestibulo-ocular reflex excitation arising from semicircular canals of rabbits. Exp Brain Res 24, 257–271, 1976.
434. Ito M, Nisimaru N, Yamamoto M. Specific patterns of neuronal connexions involved in the control of the rabbit's vestibulo-ocular reflexes by the cerebellar flocculus. J Physiol (Lond) 265, 833–854, 1977.
435. Ito Y, Gresty MA. Shift of subjective reference and visual orientation during slow pitch tilt for the seated human subject. Brain Res Bull 40, 417–421, 1996.
436. Iwasaki S, Ito K, Abbey K, Murofushi T. Prediction of canal paresis using head-shaking nystagmus test. Acta Otolaryngol 124, 803–806, 2004.
437. Living without a balancing mechanism. N Engl J Med 246, 458–460, 1952.
438. Jaeger R, Haslwanter T. Otolith responses to dynamical stimuli: results of a numerical investigation. Biol Cybern 90, 165–175, 2004.
439. Jaeger R, Takagi A, Haslwanter T. Modeling the relation between head orientations and otolith responses in humans. Hear Res 173, 29–42, 2002.
440. Jahn K, Naessl A, Schneider E, et al. Inverse U-shaped curve for age dependency of torsional eye movement responses to galvanic vestibular stimulation. Brain 126, 1579–1589, 2003.
441. Jahn K, Naessl A, Strupp M, et al. Torsional eye movement responses to monaural and binaural galvanic vestibular stimulation: side-to-side asymmetries. Ann N Y Acad Sci 1004, 485–489, 2003.
442. Jáuregui-Renaud K, Faldon M, Clarke A, Bronstein AM, Gresty MA. Skew deviation of the eyes in normal human subjects induced by semicircular canal stimulation. Neurosci Lett 235, 135–137, 1996.
443. Jauregui-Renaud K, Faldon ME, Gresty MA, Bronstein AM. Horizontal ocular vergence and the three-dimensional response to whole-body roll motion. Exp Brain Res 136, 79–92, 2001.
444. Jell RM, Ireland DJ, Lafortune S. Human optokinetic afternystagmus: effects of repeated stimulation. Acta Otolaryngol (Stockh) 99, 95–101, 1985.
445. Jenkins HA, Cohen HS, Kimball KT. Long-term vestibulo-ocular reflex changes in patients with vestibular ablation. Acta Otolaryngol 120, 187–191, 2000.
446. Johnston JL, Sharpe JA. The initial vestibulo-ocular reflex and its visual enhancement and cancellation in humans. Exp Brain Res 99, 302–308, 1994.
447. Jombik P, Bahyl V. Short latency responses in the averaged electro-oculogram elicited by vibrational impulse stimuli applied to the skull: could they reflect vestibulo-ocular reflex function? J Neurol Neurosurg Psychiatry 76, 222–228, 2005.
448. Jürgens R, Mergner T. Interaction between cervico-ocular and vestibulo-ocular reflexes in normal adults. Exp Brain Res 77, 381–390, 1989.
449. Kahane P, Hoffmann D, Minotti L, Berthoz A. Reappraisal of the human vestibular cortex by cortical electrical stimulation study. Ann Neurol 54, 615–624, 2003.
450. Kamei T, Iizuka T. Prediction of vertigo recurrences in Meniere's disease by the head-shaking test. Int Tinnitus J 5, 47–49, 1999.
451. Kamura E, Yagi T. Three-dimensional analysis of eye movements during off vertical axis rotation in patients with unilateral labyrinthine loss. Acta Otolaryngol 121, 225–228, 2001.
452. Kanayama R, Bronstein AM, Gresty MA, et al. Perceptual studies in patients with vestibular neurectomy. Acta Otolaryngol (Stockh) Suppl 520, 408–411, 1995.
453. Kansaku K, Hashimoto K, Muraki S, et al. Retinotopic hemodynamic activation of the human V5/MT area during optokinetic responses. NeuroReport 12, 3891–3895, 2001.
454. Kaplan PW, Tusa RJ. Neurophysiologic and clinical correlations of epileptic nystagmus. Neurology 43, 2508–2514, 1993.
455. Karlberg M, AW ST, Black RA, et al. Vibration-induced ocular torsion and nystagmus after unilateral vestibular deafferentation. Brain 126, 956–964, 2003.
456. Karlberg M, Magnusson M. Asymmetric optokinetic after-nystagmus induced by active or passive sustained head rotations. Acta Otolaryngol (Stockh) 116, 647–651, 1996.
457. Karnath H-O, Sievering D, Fetter M. The interactive contribution of neck muscle proprioception and vestibular stimulation to subjective "straight ahead" orientation in man. Exp Brain Res 101, 140–146, 1994.
458. Kasai T, Zee DS. Eye-head coordination in labyrinthine-defective human beings. Brain Res 144, 123–141, 1978.
458a. Kassardjian CD, Tan YF, Chung JY, Heskin R, Peterson MJ, Broussard DM. The site of a motor memory shift with consolidation. J Neurosci 25, 7979–7985, 2005.
459. Katsarkas A, Galiana HL. Bechterew's phenomenon in human. Acta Otolaryngol (Stockh) Suppl 406, 95–100, 1984.
460. Katsarkas A, Smith H, Galiana H. Head-shaking nystagmus (HSN): the theoretical explanation and the experimental proof. Acta Otolaryngol 120, 177–181, 2000.
461. Katz E, Vianney de Jong JMB, Buettner-Ennever J, Cohen B. Effects of midline medullary lesions on velocity storage and the vestibulo-ocular reflex. Exp Brain Res 87, 505–520, 1991.
462. Kelders WP, Kleinrensink GJ, van der Geest JN, et al. Compensatory increase of the cervico-ocular reflex with age in healthy humans. J Physiol 553, 311–317, 2003.
463. Kenmochi M, Ohashi T, Nishino H, Sato S. Cortical potentials evoked by horizontal rotatory stimulation: the effects of angular acceleration. Acta Otolaryngol 123, 923–927, 2003.
464. Kevetter GA, Leonard RB, Newlands SD, Perachio AA. Central distribution of vestibular afferents that innervate the anterior or lateral semicircular canal in the mongolian gerbil. J Vestib Res 14, 1–15, 2004.
465. Khater TT, Baker JF, Peterson BW. Dynamics of adaptive change in human vestibulo-ocular reflex direction. J Vestib Res 1, 23–29, 1990.
466. Kim JI, Somers JT, Stahl JS, Bhidayasiri R, Leigh RJ. Vertical nystagmus in normal subjects: effects of head position, nicotine and scopolamine. J Vestib Res 10, 291–300, 2000.
467. Kim JS, Ahn KW, Moon SY, et al. Isolated perverted head-shaking nystagmus in focal cerebellar infarction. Neurology 64, 575–576, 2005.
468. Kim JS, Sharpe JA. The vertical vestibulo-ocular reflex, and its interaction with vision during active head motion: effects of aging. J Vestib Res 11, 3–12, 2001.
469. King J, Zheng Y, Liu P, Darlington CL, Smith PF. NMDA and AMPA receptor subunit protein expression in the rat vestibular nucleus following unilateral labyrinthectomy. NeuroReport 13, 1541–1545, 2002.
470. Kitahara T, Fukushima M, Takeda N, Saika T, Kubo T. Effects of pre-flocculectomy on Fos expression and NMDA receptor-mediated neural circuits in the central vestibular system after unilateral labyrinthectomy. Acta Otolaryngol 120, 866–871, 2000.
471. Kitahara T, Fukushima M, Takeda N, et al. Role of cholinergic mossy fibers in vestibular nuclei in the development of vestibular compensation. Acta Otolaryngol Suppl 545, 101–104, 2001.
472. Kitahara T, Kondoh K, Morihana T, et al. Steroid effects on vestibular compensation in human. Neurol Res 25, 287–291, 2003.
473. Kitahara T, Takeda N, Saika T, Kubo T, Kiyama H. Role of the flocculus in the development of vestibular compensation: immunohistochemical studies with retrograde tracing and flocculectomy using fos expression as a marker in the rat brainstem. Neuroscience 76, 571–580, 1997.
474. Klam F, Graf W. Vestibular signals of posterior parietal cortex neurons during active and passive head movements in macaque monkeys. Ann N Y Acad Sci 1004, 271–282, 2003.
475. Kluge M, Beyenburg S, Fernandez G, Elger CE. Epileptic vertigo: evidence for vestibular representation in human frontal cortex. Neurology 55, 1906–1908, 2000.
476. Koizuka I. Adaptive plasticity in the otolith-ocular reflex. Auris Nasus Larynx 30 Suppl, S3–S6, 2003.
477. Koizuka I, Furman JM, Mendoza JC. Plasticity of responses to off-vertical axis rotation. Acta Otolaryngol (Stockh) 117, 321–324, 1997.
478. Konen CS, Kleiser R, Seitz RJ, Bremmer F. An fMRI study of optokinetic nystagmus and smooth-pursuit eye movements in humans. Exp Brain Res 165, 203–216, 2005.
479. Kramer PD, Roberts DC, Shelhamer M, Zee DS. A versatile stereoscopic visual display system for vestibular and oculomotor research. J Vestib Res 8, 363–380, 1998.
480. Kramer PD, Shelhamer M, Peng GCY, Zee DS. Context-specific short-term adaptation of the phase of the vestibulo-ocular reflex. Exp Brain Res 120, 184–192, 1998.
481. Kramer PD, Shelhamer M, Zee DS. Short-term adaptation of the phase of the vestibulo-ocular reflex (VOR) in normal human subjects. Exp Brain Res 106, 318–326, 1995.
482. Krauzlis RJ, Lisberger SG. Simple spike responses of gaze velocity Purkinje cells in the floccular lobe of the monkey during the onset and offset of pursuit eye movements. J Neurophysiol 72, 2045–2050, 1994.
483. Krauzlis RJ, Lisberger SJ. Directional organization of eye movement and visual signals in the floccular lobe of the monkey cerebellum. Exp Brain Res 109, 289–302, 1996.
484. Kudo K, Yoshida M, Makishima K. Reverse optokinetic after-nystagmus generated by gaze fixation during optokinetic stimulation. Acta Otolaryngol 122, 37–42, 2002.
485. Kuki Y, Hirata Y, Blazquez PM, Heiney SA, Highstein SM. Memory retention of vestibuloocular reflex motor learning in squirrel monkeys. NeuroReport 15, 1007–1011, 2004.
486. Kushiro K, Dai M, Kunin M, et al. Compensatory and orienting eye movements induced by off-vertical axis rotation (OVAR) in monkeys. J Neurophysiol 88, 2445–2462, 2002.
487. Lackner JR, DiZio P. Vestibular, proprioceptive, and haptic contributions to spatial orientation. Annu Rev Psychol 56, 115–147, 2005.
488. Lafortune SH, Ireland DJ, Jell RM, DuVal L. Human optokinetic nystagmus. Stimulus velocity dependence of the two-component decay model and involvement of pursuit. Acta Otolaryngol (Stockh) 101, 183–192, 1986.
489. Langer T, Fuchs A, Chubb M, Scudder C, Lisberger S. Floccular efferents in the rhesus macaque as revealed by autoradiography and horseradish peroxidase. J Comp Neurol 235, 26–37, 1985.
490. Langer T, Fuchs A, Scudder C, Chubb M. Afferents to the flocculus of the cerebellum in the rhesus macaque as revealed by retrograde transport of horseradish peroxidase. J Comp Neurol 235, 1–25, 1985.
491. Lasker DM, Backous DD, Lysakowski A, Davis GL, Minor LB. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. II. Responses after canal plugging. J Neurophysiol 82, 1271–1285, 1999.

492. Lasker DM, Hullar TE, Minor LB. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. III. Responses after labyrinthectomy. J. Neurophysiol. 83, 2482–2496, 2000.
493. Lasker DM, Ramat S, Carey JP, Minor LB. Vergence-mediated modulation of the human horizontal angular VOR provides evidence of pathway-specific changes in VOR dynamics. Ann N Y Acad Sci 956, 324–337, 2002.
494. Lee C, Zee DS, Straumann D. Saccades from torsional offset positions back to listing's plane. J Neurophysiol 83, 3241–3253, 2000.
495. Lee H, Cho YW. A case of isolated nodulus infarction presenting as a vestibular neuritis. J Neurol Sci 221, 117–119, 2004.
496. Lee H, Yi HA, Cho YW, et al. Nodulus infarction mimicking acute peripheral vestibulopathy. Neurology 60, 1700–1702, 2003.
497. Lehnen N, Aw ST, Todd MJ, Halmagyi GM. Head impulse test reveals residual semicircular canal function after vestibular neurectomy. Neurology 62, 2294–2296 ,2004.
498. Leigh RJ. Human vestibular cortex. Ann Neurol 35, 383–384, 1994.
499. Leigh RJ, Brandt T. A reevaluation of the vestibulo-ocular reflex: new ideas of its purpose, properties, neural substrate, and disorders. Neurology 43, 1288–1295, 1993.
500. Leigh RJ, Robinson DA, Zee DS. A hypothetical explanation for periodic alternating nystagmus: instability in the optokinetic-vestibular system. Ann N Y Acad Sci 374, 619–635, 1981.
501. Leigh RJ, Zee DS. Eye movements of the blind. Invest Ophthalmol Vis Sci 19, 328–331, 1980.
502. LeLiever WC, Correia MJ. Further observations on the effects of head position on vertical OKN and OKAN in normal subjects. Otolaryngol Head Neck Surg 97, 275–281, 1987.
503. Lempert T, Gianna C, Brookes G, Bronstein A, Gresty M. Horizontal otolith-ocular responses in humans after unilateral vestibular deafferentation. Exp Brain Res 118, 533–540, 1998.
504. Lempert T, Gresty MA, Bronstein AM. Horizontal linear vestibulo-ocular reflex testing in patients with peripheral vestibular disorders. Ann N Y Acad Sci 871, 232–247, 1999.
505. Lewis RF, Clendaniel RA, Zee DS. Vergence-dependent adaptation of the vestibulo-ocular reflex. Exp Brain Res 152, 335–340, 2003.
506. Li H, Dokas LA, Godfrey DA, Rubin AM. Remodeling of synaptic connections in the deafferented vestibular nuclear complex. J Vestib Res 12, 167–183, 2002.
507. Li J, Smith SS, McElligott JG. Cerebellar nitric oxide is necessary for vestibulo-ocular reflex adaptation, a sensorimotor model of learning. J Neurophysiol 74, 489–494, 1995.
508. Li YX, Hashimoto T, Tokuyama W, Miyashita Y, Okuno H. Spatiotemporal dynamics of brain-derived neurotrophic factor mRNA induction in the vestibulo-olivary network during vestibular compensation. J Neurosci 21, 2738–2748, 2001.
509. Lichtenberg BK, Young LR, Arrott AP. Human ocular counterrolling induced by varying linear accelerations. Exp Brain Res 48, 127–136, 1982.
510. Lisberger SG. Neural basis for motor learning in the vestibulo-ocular reflex of primates. III. Computational and behavioral analysis of the sites of learning. J Neurophysiol 72, 974–999, 1994.
511. Lisberger SG. Motor learning and memory in the vestibulo-ocular reflex: the dark side. Ann N Y Acad Sci 781, 525–531, 1996.
512. Lisberger SG, Miles FA, Optican LM. Frequency-selective adaptation: evidence for channels in the vestibulo-ocular reflex. J Neuroscience 3, 1234–1244, 1983.
513. Lisberger SG, Miles FA, Zee DS. Signals used to computer errors in the monkey vestibuloocular reflex: possible role of the flocculus. J Neurophysiol 52, 1140–1153, 1984.
514. Lisberger SG, Pavelko TA, Brontë-Stewart HM, Stone LS. Neural basis for motor learning in the vestibuloocular reflex of primates. II. Changes in the responses of horizontal gaze-velocity Purkinje cells in the cerebellar flocculus and ventral paraflocculus. J Neurophysiol 72, 954–973, 1994.
515. Lobel E, Kleine JF, Leroy-Willig A, et al. Cortical areas activated by bilateral galvanic vestibular stimulation. Ann N Y Acad Sci 871, 313–323, 1999.
516. Loose R, Probst T, Tucha O, et al. Vestibular evoked potentials from the vertical semicircular canals in humans evoked by roll-axis rotation in microgravity and under 1-G. Behav Brain Res 134, 131–137, 2002.
517. Lopez C, Borel L, Magnan J, Lacour M. Torsional optokinetic nystagmus after unilateral vestibular loss: asymmetry and compensation. Brain 128, 1511–1524, 2005.
518. Lopez I, Honrubia V, Baloh RW. Aging and the human vestibular nucleus. J Vestib Res 7, 77–85, 1997.
519. Lorente de Nó R. Vestibulo-ocular reflex arc. Arch Neurol Psychiatr 30, 245–291, 1933.
520. Lott LA, Post RB. Up-down asymmetry in vertical induced motion. Perception 22, 527–535, 1993.
521. Lozada AF, Aarnisalo AA, Karlstedt K, Stark H, Panula P. Plasticity of histamine H3 receptor expression and binding in the vestibular nuclei after labyrinthectomy in rat. BMC Neurosci 5, 32, 2004.
522. Luebke AE, Robinson DA. Gain changes of the cat's vestibulo-ocular reflex after flocculus deactivation. Exp Brain Res 98, 379–390, 1994.
523. Lysakowski A. In Cummings CC (ed). Otolaryngology Head & Neck Surgery. Elsevier Mosby, Phildelphia, 2005, pp 3089–3114.
524. Maas EF, Huebner WP, Seidman SH, Leigh RJ. Behavior of human horizontal vestibulo-ocular reflex in response to high-acceleration stimuli. Brain Res 499, 153–156, 1989.
525. MacDougall HG, Brizuela AE, Burgess AM, Curthoys IS, Halmagyi GM. Patient and normal three-dimensional eye-movement responses to maintained (DC) surface galvanic vestibular stimulation. Otol Neurotol 26, 500–511, 2005.
526. Magnusson AK, Tham R. Vestibulo-oculomotor behaviour in rats following a transient unilateral vestibular loss induced by lidocaine. Neuroscience 120, 1105–1114, 2003.
527. Mallinson AI, Longridge NS. Caloric response does not decline with age. J Vestib Res 14, 393–396, 2004.
528. Mandelli MJ, Misslisch H, Hess BJ. Static and dynamic properties of vergence-induced reduction of ocular counter-roll in near vision. Eur J Neurosci 21, 549–555, 2005.
529. Mandl G, Jones GM. Rapid visual vestibular interaction during visual tracking in strobe light. Brain Res 165, 133–138, 1979.
530. Markin VS, Hudspeth AJ. Gating-spring models of mechanoelectrical transduction by hair cells of the internal ear. Annu Rev Biophys Biomol Struct 24, 59–82, 1995.
531. Marti S, Straumann D, Glasauer S. The origin of downbeat nystagmus: an asymmetry in the distribution of on-directions of vertical gaze-velocity purkinje cells. Ann N Y Acad Sci 1039, 548–553, 2005.
532. Maruta J, Simpson JI, Raphan T, Cohen B. Orienting eye movements and nystagmus produced by translation while rotating (TWR). Exp Brain Res 163, 273–283, 2005.
533. Maruyama M, Fushiki H, Yasuda K, Watanabe Y. Asymmetric adaptive gain changes of the vertical vestibulo-ocular reflex in cats. Brain Res 1023, 302–308, 2004.
534. Matsuo S, Hosogai M, Nakao S. Ascending projections of posterior canal-activated excitatory and inhibitory secondary vestibular neurons to the mesodiencephalon in cats. Exp Brain Res 100, 7–17, 1994.
535. Matsuo V, Cohen B. Vertical optokinetic nystagmus and vestibular nystagmus in the monkey: up-down asymmetry and effects of gravity. Exp Brain Res 53, 197–216, 1984.
536. Matta FV, Enticott JC. The effects of state of alertness on the vestibulo-ocular reflex in normal subjects using the vestibular rotational chair. J Vestib Res 14, 387–391, 2004.
537. Mazzoni A. Internal auditory artery supply to the petrous bone. Arch Otolaryngol Head Neck Surg 81, 13–21, 1972.
538. McCabe BF, Ryu JH. Further experiments on vestibular compensation. Laryngoscope 82, 381–396, 1972.
539. McClure JA, Copp CC, Lycett P. Recovery nystagmus in Meniere's disease. Laryngoscope 91, 1727–1737, 1981.
540. McConville KM, Tomlinson RD, Na E. Behavior of eye-movement-related cells in the vestibular nuclei during combined rotational and translational stimuli. J Neurophysiol 76, 3136–3148, 1996.
541. McCrea R, Chen-Huang C, Belton T, Gdowski GT. Behavior contingent processing of vestibular sensory signals in the vestibular nuclei. Ann N Y Acad Sci 781, 292–303, 1996.
542. McCrea R, Gdowski G, Luan H. Current concepts of vestibular nucleus function: transformation of vestibular signals in the vestibular nuclei. Ann N Y Acad Sci 942, 328–344, 2001.
543. McCrea R, Strassman A, May E, Highstein S. Anatomical and physiological characteristics of vestibular neurons mediating the horizontal vestibulo-ocular reflex of the squirrel monkey. J Comp Neurol 264, 547–570, 1987.
544. McCrea RA, Luan H. Signal processing of semicircular canal and otolith signals in the vestibular nuclei during passive and active head movements. Ann N Y Acad Sci 1004 169–182, 2003.
545. McElligott JG, Beeton P, Polk J. Effect of cerebellar inactivation by lidocaine microdialysis on the vestibuloocular reflex in goldfish. J Neurophysiol 79, 1286–1294, 1998.
546. McElligott JG, Spencer RF. Neuropharmacological aspects of the vestibulo-ocular reflex. In Anderson JH, Beitz AJ (eds). Neurochemistry of the Vestibular System. CRC Press, Boca Raton, 2000, pp 199–222.
547. McHenry MQ, Angelaki DE. Primate translational vestibuloocular reflexes. II. Version and vergence responses to fore-aft motion. J Neurophysiol 83, 1648–1661, 2000.
548. McKenna GJ, Peng GC, Zee DS. Neck muscle vibration alters visually perceived roll in normals. J Assoc Res Otolaryngol 5, 25–31, 2004.
549. Medendorp WP, Van Gisbergen JA, Gielen CC. Human gaze stabilization during active head translations. J Neurophysiol 87, 295–304, 2002.
550. Medendorp WP, Van Gisbergen JA, Van PS, Gielen CC. Context compensation in the vestibuloocular reflex during active head rotations. J Neurophysiol 84, 2904–2917, 2000.
551. Melvill Jones, G. Adaptive modulation of VOR parameters by vision. In Berthoz A, Melvill Jones G (eds). Adaptive Mechanisms in Gaze Control. Elsevier, Amsterdam,1985, pp 21–50.
552. Melvill Jones G, Berthoz A, Segal B. Adaptive modification of the vestibulo-ocular reflex by mental effort in darkness. Exp Brain Res 56, 149–153, 1984.
553. Melvill Jones G, Guitton D, Berthoz A. Changing patterns of eye-head coordination during 6 h of optically reversed vision. Exp Brain Res 69, 531–544, 1988.
554. Melvill Jones G, Mandl G. Motion sickness due to vision reversal: its absence in stroboscopic light. Ann N Y Acad Sci 374, 303–311, 1981.
555. Meng H, Green AM, Dickman JD, Angelaki DE. Pursuit-vestibular interactions in brainstem neurons during rotation and translation. J Neurophysiol, 2005.
556. Meng H, et al. Morphology of physiologically identified otolith-related vestibular neurons in cats. Neurosci Lett 331, 37–40, 2002.
557. Merfeld DM. Rotation otolith tilt-translation reinterpretation (ROTTR) hypothesis: a new hypothesis to explain neurovestibular spaceflight adaptation. J Vestib Res 13, 309–320, 2003.
558. Merfeld DM. Modeling human vestibular responses during eccentric rotation and off vertical axis rotation. Acta Otolaryngol (Stockh) 520, 354–359, 1995.
559. Merfeld DM, Park S, Gianna-Poulin C, Black FO, Wood S. Vestibular perception and action employ qualitatively different mechanisms: I. Frequency response of VOR and perceptual responses during translation and tilt. J Neurophysiol 94, 186–198, 2005.
560. Merfeld DM, Park S, Gianna-Poulin C, Black FO, Wood S. Vestibular perception and action employ qualitatively different mechanisms: II. VOR and perceptual responses during combined tilt and translation. J Neurophysiol 94, 199–205, 2005.
561. Merfeld DM, Young LR. The vestibulo-ocular reflex of the squirrel monkey during eccentric rotation and roll tilt. Exp Brain Res 106, 111–122, 1995.
562. Merfeld DM, Young LR, Oman CM, Shelhamer MJ. A multdimensional model of the effect of gravity on the spatial orientation of the monkey. J Vestib Res 3, 141–161, 1993.

563. Merfeld DM, Zupan L, Peterka RJ. Humans use internal models to estimate gravity and linear acceleration. Nature 398, 615–618, 1999.
564. Merfeld DM, Zupan LH. Neural processing of gravitoinertial cues in humans. III. Modeling tilt and translation responses. J Neurophysiol 87, 819–833, 2002.
565. Merfeld DM, Zupan LH, Gifford CA. Neural processing of gravito-inertial cues in humans. II. Influence of the semicircular canals during eccentric rotation. J Neurophysiol 85, 1648–1660, 2001.
566. Mergner T, Glasauer S. A simple model of vestibular canal-otolith signal fusion. Ann N Y Acad Sci 871, 430–434, 1999.
567. Mergner T, Huber W, Becker W. Vestibular-neck interaction and transformation of sensory coordinates. J Vestib Res 7, 347–367, 1997.
568. Mergner T, Schweigart G, Muller M, Hlavacka F, Becker W. Visual contributions to human self-motion perception during horizontal body rotation. Arch Ital Biol 138, 139–166, 2000.
569. Mergner T, Wertheim A, Rumberger A. Which retinal and extra-retinal information is crucial for circular vection? Arch Ital Biol 138, 123–138, 2000.
570. Mesland BS, Finlay AL, Wertheim AH, et al. Object motion perception during ego-motion: patients with a complete loss of vestibular function vs. normals. Brain Res Bull 40, 459–465, 1996.
571. Michel J, Dumas G, Lavieille JP, Charachon R. Diagnostic value of vibration-induced nystagmus obtained by combined vibratory stimulation applied to the neck muscles and skull of 300 vertiginous patients. Rev Laryngol Otol Rhinol (Bord) 122, 89–94, 2001.
572. Migliaccio AA, Della Santina CC, Carey JP, Minor LB, Zee DS. The effect of binocular eye position and head rotation plane on the human torsional vestibuloocular reflex. Vision Res, 2006.
573. Migliaccio AA, Cremer PD, Aw ST, et al. Vergence-mediated changes in the axis of eye rotation during the human vestibulo-ocular reflex can occur independent of eye position. Exp Brain Res 151, 238–248, 2003.
574. Migliaccio AA, Halmagyi GM, Mcgarvie LA, Cremer PD. Cerebellar ataxia with bilateral vestibulopathy: description of a syndrome and its characteristic clinical sign. Brain 127, 280–293, 2004.
575. Migliaccio AA, Minor LB, Carey JP. Vergence-mediated modulation of the human horizontal vestibulo-ocular reflex is eliminated by a partial peripheral gentamicin lesion. Exp Brain Res 159, 92–98, 2004.
575a. Migliaccio AA, Schubert MC, Clendaniel R, Carey JP, Della Santina CC, Minor LB, Zee DS. Axis of eye rotation changes with head-pitch orientation during head impulses about Earth-vertical. J Assoc Res Otolaryngol 2006.
576. Miles FA. The sensing of rotational and translational optic flow by the primate optokinetic system. In Miles FA, Wallman J (eds). Visual Motion and its Role in the Stabilization of Gaze. Elsevier, Amsterdam, 1993, pp 393–403.
577. Miles FA. The neural processing of 3-D visual information: evidence from eye movements. Eur J Neurosci 10, 811–822, 1998.
578. Miles FA, Braitman DJ, Dow BA. Long-term adaptive changes in primate vestibuloocular reflex. IV. Electrophysiological observations in flocculus of adapted monkeys. J Neurophysiol 43, 1477–1493, 1980.
579. Minagar A, Sheremata WA, Tusa RJ. Perverted head-shaking nystagmus: a possible mechanism. Neurology 57, 887–889, 2001.
580. Minor LB. Labyrinthine fistulae: pathobiology and management. Curr Opin Otolaryngol Head Neck Surg 11, 340–346, 2003.
581. Minor LB, Goldberg JM. Vestibular-nerve inputs to the vestibulo-ocular reflex: a functional ablation study in the squirrel monkey. J Neurosci 11, 1636–1648, 1991.
582. Minor LB, Haslwanter T, Straumann D, Zee DS. Hyperventilation-induced nystagmus in patients with vestibular schwannoma. Acta Otolaryngol (Stockh), 1998.
583. Minor LB, Lasker DM, Backous DD, Hullar TE. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. I. Normal responses. J Neurophysiol 82, 1254–1270, 1999.
584. Minor LB, McCrea R, Goldberg JM. Dual projections of secondary vestibular axons in the medial longitudinal fasciculus to extraocular motor nuclei and the spinal cord of the squirrel monkey. Exp Brain Res 83, 9–21, 1990.
585. Misslisch H, Hess BJ. Combined influence of vergence and eye position on three-dimensional vestibulo-ocular reflex in the monkey. J Neurophysiol 88, 2368–2376, 2002.
586. Misslisch H, Tweed D. Torsional dynamics and cross-coupling in the human vestibulo-ocular reflex during active head rotation. J Vestib Res 10, 119–125, 2000.
587. Misslisch H, Tweed D, Fetter M, Sievering D, Koenig E. Rotational kinematics of the human vestibuloocular reflex. III. Listing's law. J Neurophysiol 72, 2490–2502, 1994.
588. Misslisch H, Tweed D, Hess BJ. Stereopsis outweighs gravity in the control of the eyes. J Neurosci 21, RC126, 2001.
589. Miyamoto T, Fukushima K, Takada T, DE Waele C, Vidal PP. Saccular projections in the human cerebral cortex. Ann N Y Acad Sci 1039, 124–131, 2005.
590. Moller C, Odkvist LM, White V, Cyr D. The plasticity of compensatory eye movements in rotatory tests. I. The effects of alertness and eye closure. Acta Otolaryngol (Stockh) 109, 15–24, 1990.
591. Moller C, White V, Odkvist L. Plasticity of compensatory eye movements in rotatory tests. II. The effects of voluntary, visual, imaginary, auditory and proprioceptive mechanisms. Acta Otolaryngol (Stockh) 109, 168–178, 1990.
592. Morita M, Imai T, Kazunori S, et al. A new rotational test for vertical semicircular canal function. Auris Nasus Larynx 30, 233–237, 2003.
593. Morrow MJ, Sharpe JA. The effects of head and trunk position on torsional vestibular and optokinetic eye movements in humans. Exp Brain Res 95, 144–150, 1993.
594. Murai N, Tsuji J, Ito J, Mishina M, Hirano T. Vestibular compensation in glutamate receptor delta-2 subunit knockout mice: dynamic property of vestibulo-ocular reflex. Eur Arch Otorhinolaryngol 261, 82–86, 2004.

595. Murasugi CM, Howard IP. Up-down asymmetry in human vertical optokinetic nystagmus and afternystagmus: contributions of the central and peripheral retinae. Exp Brain Res 77, 183–192, 1989.
596. Murofushi T, Halmagyi GM, Yavor RA, Colebatch JG. Absent vestibular evoked myogenic potentials in vestibular neurolabyrinthitis. An indicator of inferior vestibular nerve involvement? Arch Otolaryngol Head Neck Surg 122, 845–848, 1996.
597. Murofushi T, Monobe H, Ochiai A, Ozeki H. The site of lesion in "vestibular neuritis": study by galvanic VEMP. Neurology 61, 417–418, 2003.
598. Murofushi T, Takai Y, Iwasaki S, Matsuzaki M. VEMP recording by binaural simultaneous stimulation in subjects with vestibulo-cochlear disorders. Eur Arch Otorhinolaryngol, 2005.
599. Musallam WS, Tomlinson RD. Model for the translational vestibulooocular reflex (VOR). J Neurophysiol 82, 2010–2014, 1999.
600. Myers SF. Patterns of low-frequency rotational responses in bilateral caloric weakness patients. J Vestib Res 2, 123–131, 1992.
601. Naganuma H, Tokumasu K, Okamoto M, Hashimoto S, Yamashina S. Three-dimensional analysis of morphological aspects of the human saccular macula. Ann Otol Rhinol Laryngol 110, 1017–1024, 2001.
602. Naganuma H, Tokumasu K, Okamoto M, Hashimoto S, Yamashina S. Three-dimensional analysis of morphological aspects of the human utricular macula. Ann Otol Rhinol Laryngol 112, 419–424, 2003.
603. Nagao S. Different roles of flocculus and ventral paraflocculus for oculomotor control in the primate. NeuroReport 3, 13–16, 1992.
604. Nagao S, Kitamura T, Nakamura N, Hiramatsu T, Yamada J. Differences of the primate flocculus and ventral paraflocculus in the mossy and climbing fiber input organization. J Comp Neurol 382, 480–498, 1997.
605. Nagao S, Kitamura T, Nakamura N, Hiramatsu T, Yamada J. Location of efferent terminals of the primate flocculus and ventral paraflocculus revealed by anterograde axonal transport methods. Neurosci Res 27, 257–269, 1997.
606. Nagao S, Kitazawa H. Effects of reversible shutdown of the monkey flocculus on the retention of adaptation of the horizontal vestibulo-ocular reflex. Neuroscience 118, 563–570, 2003.
607. Naito Y, Newman A, Lee WS, Beykirch K, Honrubia V. Projections of the individual vestibular end-organs in the brain stem of the squirrel monkey. Hearing Res 87, 141–155, 1995.
608. Naito Y, Tateya I, Hirano S, et al. Cortical correlates of vestibulo-ocular reflex modulation: a PET study. Brain 126, 1562–1578, 2003.
609. Nakamagoe K, Iwamoto Y, Yoshida K. Evidence for brainstem structures participating in oculomotor integration. Science 288, 857–859, 2000.
610. Nakamura T, Bronstein AM. The perception of head and neck angular displacement in normal and labyrinthine-defective subjects—A quantitative study using a 'remembered saccade' technique. Brain 118, 1157–1168, 1995.
611. Nelson JR. The minimal ice water caloric test. Neurology 19, 577–585, 1969.
612. Newlands SD, Dara S, Kaufman GD. Relationship of static and dynamic mechanisms in vestibuloocular reflex compensation. Laryngoscope 115, 191–204, 2005.
613. Newlands SD, Hesse SV, Haque A, Angelaki DE. Head unrestrained horizontal gaze shifts after unilateral labyrinthectomy in the rhesus monkey. Exp Brain Res 140, 25–33, 2001.
614. Newlands SD, Vrabec JT, Purcell IM, et al. Central projections of the saccular and utricular nerves in macaques. J Comp Neurol 466, 31–47, 2003.
615. Ng M, Davis LL, O'Leary DP. Autorotation test of the horizontal vestibulo-ocular reflex in Meniere's disease. Otolaryngol Head Neck Surg 109, 399–412, 1993.
616. Nogami K, Uemura T, Iwamoto M. VOR gain and phase in active head rotation tests of normal subjects and patients with peripheral labyrinthine lesions. Acta Otolaryngol (Stockh) 107, 333–337, 1989.
617. Nuti D, Mandala M, Broman AT, Zee DS. Acute vestibular neuritis: prognosis based upon bedside clinical tests (thrusts and heaves). Ann N Y Acad Sci 1039, 359–367, 2005.
618. O'Leary DP, Davis LL, Li SA. Predictive monitoring of high-frequency vestibulo-ocular reflex rehabilitation following gentamicin ototoxicity. Acta Otolaryngol (Stockh) 202–204, 1995.
619. O'Leary DP, Davis LL, Maceri DR. Vestibular autorotation test asymmetry analysis of acoustic neuromas. Otolaryngol Head Neck Surg 104, 102–109, 1991.
620. Oas J, Baloh RW. Vertigo and the anterior inferior cerebellar artery syndrome. Neurology 42, 2274–2279, 1992.
621. Ogawa Y, Kushiro K, Zakir M, Sato H, Uchino Y. Neuronal organization of the utricular macula concerned with innervation of single vestibular neurons in the cat. Neurosci Lett 278, 89–92, 2000.
622. Ohgaki T, Curthoys IS, Markham CH. Morphology of physiologically identified second-order vestibular neurons in the cat, with intracellularly injected HRP. J Comp Neurol 276, 387–411, 1988.
623. Ohki M, Murofushi T, Nakahara H, Sugasawa K. Vibration-induced nystagmus in patients with vestibular disorders. Otolaryngol Head Neck Surg 129, 255–258, 2003.
624. Ohki Y, Shimazu H, Suzuki I. Excitatory input to burst neurons from the labyrinth and its mediating pathway in the cat: location and functional characteristics of burster-driving neurons. Exp Brain Res 72, 457–472, 1988.
625. Okiyama R, Shimizu N. Optokinetic response and adaptation of the vestibulo-ocular reflex (VOR) in a patient with chronic cortical blindness. Acta Otolaryngol Suppl 481, 556–558, 1991.
626. Ono S, Kushiro A, Zakir M, et al. Properties of utricular and saccular nerve-activated vestibulocerebellar neurons in cats. Exp Brain Res 134, 1–8, 2000.
627. Oohira A, Zee DS. Disconjugate ocular motor adaptation in rhesus monkey. Vision Res 32, 489–497, 1992.
628. Ooi D, Cornell ED, Curthoys IS, Burgess AM, MacDougall HG. Convergence reduces ocular counterroll (OCR) during static roll-tilt. Vision Res 44, 2825–2833, 2004.
629. Ostrowski VB, Byskosh A, Hain TC. Tullio phenomenon with dehiscence of the superior semicircular canal. Otol Neurotol 22, 61–65, 2001.

630. Paige GD. Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. Exp Brain Res 98, 355–372, 1994.
631. Paige GD. Senescence of human visual-vestibular interactions. 1. Vestibulo-ocular reflex and adaptive plasticity with aging. J Vestib Res 2, 133–151, 1992.
632. Paige GD. Caloric responses after horizontal canal inactivation. Acta Otolaryngol (Stockh) 100, 321–327, 1981.
633. Paige GD. Otolith function: basis for modern testing. Ann N Y Acad Sci 956, 314–323, 2002.
634. Paige GD. The influence of target distance on eye movement responses during vertical linear motion. Exp Brain Res 77, 585–593, 1989.
635. Paige GD, Barnes GR, Telford L, Seidman SH. The influence of sensori-motor context on the linear vestibulo-ocular reflex. Ann N Y Acad Sci 781, 322–331, 1996.
636. Paige GD, Sargent EW. Visually-induced adaptive plasticity in the human vestibulo-ocular reflex. Exp Brain Res 84, 25–34, 1991.
637. Paige GD, Seidman SH. Characteristics of the VOR in response to linear acceleration. Ann N Y Acad Sci 871, 123–135, 1999.
638. Paige GD, Telford L, Seidman SH, Barnes GR. Human vestibuloocular reflex and its interactions with vision and fixation distance during linear and angular head movement. J Neurophysiol 80, 2391–2404, 1998.
639. Paige GD, Tomko DL. Eye movement responses to linear head motion in the squirrel monkey. I. Basic characteristics. J Neurophysiol 65, 1170–1182, 1991.
640. Paige GD, Tomko DL. Eye movement responses to linear head motion in the squirrel monkey. II. Visual-vestibular interactions and kinematic considerations. J Neurophysiol 65, 1183–1196, 1991.
641. Palla A, Bockisch CJ, Bergamin O, Straumann D. Residual torsion following ocular counterroll. Ann N Y Acad Sci 1039, 81–87, 2005.
642. Palla A, Marti S, Straumann D. Head-shaking nystagmus depends on gravity. J Assoc Res Otolaryngol 6, 1–8, 2005.
643. Palla A, Straumann D. Recovery of the high-acceleration vestibulo-ocular reflex after vestibular neuritis. J Assoc Res Otolaryngol 5, 427–435, 2004.
644. Palla A, Straumann D, Obzina H. Eye-position dependence of three-dimensional ocular rotation-axis orientation during head impulses in humans. Exp Brain Res 129, 127–133 1999.
645. Pansell T, Tribukait A, Bolzani R, Schworm HD, Ygge J. Drift in ocular counterrolling during static head tilt. Ann N Y Acad Sci 1039, 554–557, 2005.
646. Pansell T, Ygge J, Schworm HD. Conjugacy of torsional eye movements in response to a head tilt paradigm. Invest Ophthalmol Vis Sci 44, 2557–2564, 2003.
647. Partsalis AM, Highstein SM. Role of the Y group of the vestibular nuclei in motor learning or plasticity of the vestibulo-ocular reflex in the squirrel monkey. Ann N Y Acad Sci 781, 489–498, 1996.
648. Pastor AM, De La Cruz RR, Baker R. Cerebellar role in adaptation of the goldfish vestibuloocular reflex. J Neurophysiol 72, 1383–1394, 1994.
649. Payman RN, Wall C, Ashbernal R. Otolith function tests in patients with unilateral vestibular lesions. Acta Otolaryngol (Stockh) 115, 715–724, 1995.
650. Penfield W. Vestibular sensation and the cerebral cortex. Ann Otol Rhinol Laryngol 66, 691–698, 1957.
651. Peng GC, Baker JF, Peterson BW. Dynamics of directional plasticity in the human vertical vestibulo-ocular reflex. J Vestib Res 4, 453–460, 1994.
652. Peng GC, Minor LB, Zee DS. Gaze position corrective eye movements in normal subjects and in patients with vestibular deficits. Ann N Y Acad Sci 1039, 337–348, 2005.
653. Peng GC, Zee DS, Minor LB. Phase-plane analysis of gaze stabilization to high acceleration head thrusts: a continuum across normal subjects and patients with loss of vestibular function. J Neurophysiol 91, 1763–1781, 2004.
654. Perez N. Vibration induced nystagmus in normal subjects and in patients with dizziness. A videonystagmography study. Rev Laryngol Otol Rhinol (Bord) 124, 85–90, 2003.
655. Perez N, Martin E, Romero MD, Garcia-Tapia R. Influence of canal paresis and compensation on gain and time constant of nystagmus slow-phase velocity to yaw-axis rotation. Acta Otolaryngol 121, 715–723, 2001.
656. Perez N, Rama-Lopez J. Head-impulse and caloric tests in patients with dizziness. Otol Neurotol 24, 913–917, 2003.
657. Perez P, Lorente JL, Gomez JR, et al. Functional significance of peripheral head-shaking nystagmus. Laryngoscope 114, 1078–1084, 2004.
658. Peterka RJ. Response characteristics of the human torsional vestibuloocular reflex. J Vestib Res 3, 877–879, 1992.
659. Peterka RJ, Black FO, Schoenhoff MB. Age-related changes in human vestibulo-ocular and optokinetic reflexes: pseudorandom rotation tests. J Vestib Res 1, 61–71, 1990.
660. Peterka RJ, Black FO, Schoenhoff MB. Age-related changes in human vestibulo-ocular reflex: sinusoidal rotation and caloric tests. J Vestib Res 1, 49–59, 1990.
661. Peterka RJ, Gianna-Poulin CC, Zupan LH, Merfeld DM. Origin of orientation-dependent asymmetries in vestibulo-ocular reflexes evoked by caloric stimulation. J Neurophysiol 92, 2333–2345, 2004.
662. Peters B, Bloomberg J. Dynamic visual acuity using "far" and "near" targets. Acta Otolaryngol 125, 353–357, 2005.
663. Peterson BW, Kinney GA, Quinn KJ, Slater NT. Potential mechanisms of plastic adaptive changes in the vestibulo-ocular reflex. Ann N Y Acad Sci 781, 499–512, 1996.
664. Petropoulos AE, Wall C, III Oman CM. Yaw sensory rearrangement alters pitch vestibulo-ocular reflex responses. Acta Otolaryngol (Stockh) 117, 647–656, 1997.
665. Pierrot-Deseilligny C, Milea D. Vertical nystagmus: clinical facts and hypotheses. Brain 148, 1237–1246, 2005.
666. Popov KE, Lekhel H, Faldon M, Bronstein AM, Gresty MA. Visual and oculomotor responses induced by neck vibration in normal subjects and labyrinthine-defective patients. Exp Brain Res 128, 343–352, 1999.
667. Powell KD, Peterson BW, Baker JF. Phase-shifted direction adaptation of the vestibulo-ocular reflex in cat. J Vestib Res 6, 277–293, 1996.
668. Powell KD, Quinn KJ, Rude SA, Peterson BW, Baker JF. Frequency dependence of cat vestibulo-ocular reflex direction adaptation: single frequency and multifrequency rotations. Brain Res 550, 137–141, 1991.
669. Precht W. Neuronal Operations in the Vestibular System. Springer, New York, 1978.
670. Precht W. Vestibular mechanisms. Annu Rev Neurosci 2, 265–289, 1979.
671. Precht W. In Lennerstrand G, Zee DS, Keller EL (eds). Functional Basis of Ocular Motility Disorders. Pergamon Press, Oxford, 1982, pp 297–302.
672. Prepageran N, Kisilevsky V, Tomlinson D, Ranalli P, Rutka J. Symptomatic high frequency/acceleration vestibular loss: consideration of a new clinical syndrome of vestibular dysfunction. Acta Otolaryngol 125, 48–54, 2005.
673. Priesol AJ, Jones GE, Tomlinson RD, Broussard DM. Frequency-dependent effects of glutamate antagonists on the vestibulo-ocular reflex of the cat. Brain Res 857, 252–264, 2000.
674. Probst T, Brandt T, Degner D. Object-motion detection affected by concurrent self-motion perception: psychophysics of a new phenomenon. Behav Brain Sci 22, 1–11, 1986.
675. Pulaski PD, Zee DS, Robinson DA. The behavior of the vestibuloocular reflex at high velocities of head movement. Brain Res 22, 159–161, 1981.
676. Purcell IM, Kaufman GD, Shinder ME, Perachio AA. Retrograde double-labeling studies of vestibular efferent neurons projecting to the flocculus [abstract]. Soc Neurosci Abstr 27, 1290, 1997.
677. Quinn KJ, Didier AJ, Baker JF, Peterson BW. Modeling learning in brain stem and cerebellar sites responsible for VOR plasticity. Brain Res Bull 46, 333–346, 1998.
678. Quinn KJ, Helminski JO, Didier AJ, Baker JF, Peterson BW. Changes in sensitivity of vestibular nucleus neurons induced by cross-axis adaptation of the vestibulo-ocular reflex in the cat. Brain Res 718, 176–180, 1996.
679. Rabbitt RD, Boyle R, Holstein GR, Highstein SM. Hair-cell versus afferent adaptation in the semicircular canals. J Neurophysiol 93, 424–436, 2005.
680. Radtke A, Bronstein AM, Gresty MA, et al. Paroxysmal alternating skew deviation and nystagmus after partial destruction of the uvula. J Neurol Neurosurg Psychiatry 70, 790–793, 2001.
681. Ramachandran R, Lisberger SG. Normal performance and expression of learning in the vestibulo-ocular reflex (VOR) at high frequencies. J Neurophysiol 93, 2028–2038, 2005.
682. Ramat S, Straumann D, Zee DS. The interaural translation VOR: suppression, enhancement and cognitive control. J Neurophysiol 94, 2391–2402, 2005.
683. Ramat S, Zee DS. Ocular motor responses to abrupt interaural head translation in normal humans. J Neurophysiol 90, 887–902, 2003.
684. Ramat S, Zee DS. Binocular coordination in fore/aft motion. Ann N Y Acad Sci 1039, 36–53, 2005.
685. Ramat S, Zee DS, Minor LB. Translational vestibulo-ocular reflex evoked by a "head heave" stimulus. Ann N Y Acad Sci 942, 95–113, 2001.
686. Rambold H, Churchland A, Selig Y, Jasmin L, Lisberger SG. Partial ablations of the flocculus and ventral paraflocculus in monkeys cause linked deficits in smooth pursuit eye movements and adaptive modification of the VOR. J Neurophysiol 87, 912–924, 2002.
687. Rambold H, Heide W, Sprenger A, Haendler G, Helmchen C. Perilymph fistula associated with pulse-synchronous eye oscillations. Neurology 56, 1769–1771, 2001.
688. Rambold H, Helmchen C. Spontaneous nystagmus in dorsolateral medullary infarction indicates vestibular semicircular canal imbalance. J Neurol Neurosurg Psychiatry 76, 88–94, 2005.
689. Rambold H, Helmchen C, Buttner U. Vestibular influence on the binocular control of verticaltorsional nystagmus after lesions in the interstitial nucleus of Cajal. NeuroReport 11, 779–784, 2000.
690. Ranalli PJ, Sharpe JA. Vertical vestibulo-ocular reflex, smooth pursuit and eye-head tracking dysfunction in internuclear ophthalmoplegia. Brain 111, 1299–1317, 1988.
691. Ranalli PJ, Sharpe JA. Upbeat nystagmus and the ventral tegmental pathway of the upward vestibulo-ocular reflex. Neurology 38, 1329–1330, 198.
692. Raphan T, Cohen B. The vestibulo-ocular reflex in three dimensions. Exp Brain Res 145, 1–27, 2002.
693. Raphan T, Matsuo V, Cohen B. Velocity storage in the vestibulo-ocular reflex arc (VOR). Exp Brain Res 35, 229–248, 1979.
694. Raphan T, Wearne SL, Cohen B. Modeling the organization of the linear and angular vestibulo-ocular reflexes. Ann N Y Acad Sci 781, 348–363, 1996.
695. Raymond JL, Lisberger SG. Behavioral analysis of signals that guide learned changes in the amplitude and dynamics of the vestibulo-ocular reflex. J Neurosci 16, 7791–7802, 1996.
696. Raymond JL, Lisberger SG. Neural learning rules for the vestibulo-ocular reflex. J Neurosci 18, 9112–9129, 1998.
697. Reisman JE, Anderson JH. Compensatory eye movements during head and body rotation in infants. Brain Res 484, 119–129, 1989.
698. Rijkaart DC, van der Geest JN, Kelders WP, De Zeeuw CI, Frens MA. Short-term adaptation of the cervico-ocular reflex. Exp Brain Res 156, 124–128, 2004.
699. Ris L, Capron B, de Waele C, Vidal P-P, Godaux E. Dissociations between behavioral recovery and restoration of vestibular activity in the unilabyrinthectomized guinea-pig. J Physiol (Lond) 500, 509–522, 1997.
700. Ris L, Capron B, Vibert N, Vidal P-P, Godaux E. Modification of the pacemaker activity of vestibular neurons in brainstem slices during vestibular compensation in the guinea pig. Eur J Neurosci 13, 2234–2240, 2001.
701. Ris L, Hachemaoui M, Vibert N, et al. Resonance of spike discharge modulation in neurons of the guinea pig medial vestibular nucleus. J Neurophysiol 86, 703–716, 2001.
702. Robertson DD, Ireland DJ. Vestibular evoked myogenic potentials. J Otolaryngol 24, 3–8, 1995.
703. Robinson DA. The use of matrices in analyzing the three-dimensional behavior of the vestibulo-ocular reflex. Biol Cybern 46, 53–66, 1982.
704. Rodionov V, Zislin J, Elidan J. Imagination of body rotation can induce eye movements. Acta Otolaryngol 124, 684–689, 2004.
705. Roy FD, Tomlinson RD. Characterization of the vestibulo-ocular reflex evoked by high-velocity movements. Laryngoscope 114, 1190–1193, 2004.

706. Roy JE, Cullen KE. Vestibuloocular reflex signal modulation during voluntary and passive head movements. J Neurophysiol 87, 2337–2357, 2002.
707. Roy JE, Cullen KE. Brain stem pursuit pathways: dissociating visual, vestibular, and proprioceptive inputs during combined eye-head gaze tracking. J Neurophysiol 90, 271–290, 2003.
708. Roy JE, Cullen KE. Dissociating self-generated from passively applied head motion: neural mechanisms in the vestibular nuclei. J Neurosci 24, 2102–2111, 2004.
709. Rude SA, Baker JF. Otolith orientation and downbeat nystagmus in the normal cat. Exp Brain Res 111, 144–148, 1996.
710. Rudge P, Chambers BR. Physiological basis for enduring vestibular symptoms. J Neurol Neurosurg Psychiatry 45, 126–130, 1982.
711. Saadat D, O'Leary DP, Pulec JL, Kitano H. Comparison of vestibular autorotation and caloric testing. Otolaryngol Head Neck Surg 113, 215–222, 1995.
711a. Saj A, Honore J, Bernati T, Coello Y, Rousseaux M. Subjective visual vertical in pitch and roll in right hemispheric stroke. Stroke 36, 588–591, 2005.
712. Sakaguchi M, Taguchi K, Sato K, et al. Vestibulo-ocular reflex and visual vestibulo-ocular reflex during sinusoidal rotation in children. Acta Otolaryngol (Stockh) Suppl 528, 70–73, 1997.
713. Sakellari V, Bronstein AM, Corna S, et al. The effects of hyperventilation on postural control mechanisms. Brain 120, 1659–1673, 1997.
714. Sansom AJ, Smith PF, Darlington CL, Laverty R. Vestibular nucleus N-methyl-D-aspartate receptors contribute to spontaneous nystagmus generation following unilateral labyrinthectomy in guinea pigs. Neurosci Lett 283, 117–120, 2000.
715. Sato F, Sasaki H. Morphological correlations between spontaneously discharging primary vestibular afferents and vestibular nucleus neurons in the cat. J Comp Neurol 333, 554–566, 1993.
716. Sawyer RN, Thurston SE, Becker KR, et al. The cervico-ocular reflex of normal human subjects in response to transient and sinusoidal trunk rotations. J Vestib Res 4, 245–249, 1994.
717. Schlack A, Hoffmann KP, Bremmer F. Interaction of linear vestibular and visual stimulation in the macaque ventral intraparietal area (VIP). Eur J Neurosci 16, 1877–1886, 2002.
718. Schlack A, Sterbing-D'Angelo SJ, Hartung K, Hoffmann KP, Bremmer F. Multisensory space representations in the macaque ventral intraparietal area. J Neurosci 25, 4616–4625, 2005.
719. Schmid-Priscoveanu A, Bohmer A, Obzina H, Straumann D. Caloric and search-coil head-impulse testing in patients after vestibular neuritis. J Assoc Res Otolaryngol 2, 72–78, 2001.
720. Schmid-Priscoveanu A, Kori AA, Straumann D. Torsional vestibulo-ocular reflex during whole-body oscillation in the upright and the supine position: II. Responses in patients after vestibular neuritis. J Vestib Res 14, 353–359, 2004.
721. Schmid-Priscoveanu A, Straumann D, Kori AA. Torsional vestibulo-ocular reflex during whole-body oscillation in the upright and the supine position. I. Responses in healthy human subjects. Exp Brain Res 134, 212–219, 2000.
722. Schneider E, Glasauer S, Dieterich M, Kalla R, Brandt T. Diagnosis of vestibular imbalance in the blink of an eye. Neurology 63, 1209–1216, 2004.
722a. Schneider JP, Reinohs M, Prothmann S, et al. Subcortical right parietal AVM rotational vertigo and caloric stimulation fMRI support a parietal representation of vestibular input. J Neurol, published online, 2005.
723. Schubert MC, Das V, Tusa RJ, Herdman SJ. Cervico-ocular reflex in normal subjects and patients with unilateral vestibular hypofunction. Otol Neurotol 25, 65–71, 2004.
724. Schubert MC, Herdman SJ, Tusa RJ. Vertical dynamic visual acuity in normal subjects and patients with vestibular hypofunction. Otol Neurotol 23, 372–377, 2002.
725. Schubert MC, Minor LB. Vestibulo-ocular physiology underlying vestibular hypofunction. Phys Ther 84, 373–385, 2004.
726. Schubert MC, Tusa RJ, Grine LE, Herdman SJ. Optimizing the sensitivity of the head thrust test for identifying vestibular hypofunction. Phys Ther 84, 151–158, 2004.
727. Schultheis LW, Robinson DA. Directional plasticity of the vestibulo-ocular reflex in the cat. Ann N Y Acad Sci 374, 504–512, 1981.
728. Schwarz U, Miles FA. Ocular responses to translation and their dependence on viewing distance. I. Motion of the observer. J Neurophysiol 66, 851–864, 1991.
729. Schweigart G, Heimbrand S, Mergner T, Becker W. Perception of horizontal head and trunk rotation: modification of neck input following loss of vestibular function. Exp Brain Res 95, 533–546, 1993.
730. Schweigart G, Mergner T, Evdokimidis I, Morand S, Becker W. Gaze stabilization by optokinetic reflex (okr) and vestibulo-ocular reflex (vor) during active head rotation in man. Vision Res 12, 1643–1652, 1997.
731. Scudder C, Fuchs AF. Physiological and behavioral identification of vestibular nucleus neurons mediating the horizontal vestibuloocular reflex in trained rhesus monkeys. J Neurophysiol 68, 244–264, 1992.
732. Segal BN, Katsarkas A. Long-term deficits of goal-directed vestibulo-ocular function following total unilateral loss of peripheral vestibular function. Acta Otolaryngol (Stockh) 106, 102–110, 1988.
733. Segal BN, Katsarkas A. Goal-directed vestibulo-ocular function in man: gaze stabilization by slow-phase and saccadic eye movements. Exp Brain Res 70, 26–32, 1988.
734. Segal BN, Liben S. Modification of human velocity storage sampled during intermittently-illuminated optokinetic stimulation. Exp Brain Res 59, 515–523, 1985.
735. Seidman SH, Leigh RJ. The human torsional vestibulo-ocular reflex during rotation about an earth-vertical axis. Brain Res 504, 264–268, 1989.
736. Seidman SH, Leigh RJ, Tomsak RL, Grant MP, Dell'Osso LF. Dynamic properties of the human vestibulo-ocular reflex during head rotations in roll. Vision Res 35, 679–689, 1995.
737. Seidman SH, Paige GD, Tomko DL. Adaptive plasticity in the naso-occipital linear vestibulo-ocular reflex. Exp Brain Res 125, 485–494, 1999.
738. Seidman SH, Paige GD, Tomlinson RD, Schmitt N. Linearity of canal-otolith interaction during eccentric rotation in humans. Exp Brain Res 147, 29–37, 2002.
739. Seidman SH, Telford L, Paige GD. Vertical, torsional and horizontal eye movement responses to head roll in the squirrel monkey. Exp Brain Res 104, 218–226, 1995.
740. Sekirnjak C, Du LS. Intrinsic firing dynamics of vestibular nucleus neurons. J Neurosci 22, 2083–2095, 2002.
741. Serra A, Derwenskus J, Downey DL, Leigh RJ. Role of eye movement examination and subjective visual vertical in clinical evaluation of multiple sclerosis. J Neurol 250, 569–575, 2003.
742. Severac CA, Faldon M, Popov K, Day BL, Bronstein AM. Short-latency eye movements evoked by near-threshold galvanic vestibular stimulation. Exp Brain Res 148, 414–418, 2003.
743. Shaikh AG, Ghasia FF, Dickman JD, Angelaki DE. Properties of cerebellar fastigial neurons during translation, rotation, and eye movements. J Neurophysiol 93, 853–863, 2005.
743a. Shaikh AG, Green AM, Ghasia FF, Newlands SD, Dickman JD, Angelaki DE. Sensory convergence solves a motion ambiguity problem. Curr Biol 15, 1657–1662, 2005.
744. Shaikh AG, Meng H, Angelaki DE. Multiple reference frames for motion in the primate cerebellum. J Neurosci 24, 4491–4497, 2004.
745. Shallo-Hoffmann J, Bronstein AM. Visual motion detection in patients with absent vestibular function. Vision Res 43, 1589–1594, 2003.
746. Sharpe J, Lo A. Voluntary and visual control of the vestibuloocular reflex after cerebral hemidecortication. Ann Neurol 10, 164–172, 1981.
747. Shelhamer M, Merfeld DM, Mendoza JC. Vergence can be controlled by audio feedback, and induces downward ocular deviation. Exp Brain Res, 1994.
748. Shelhamer M, Peng GC, Ramat S, Patel V. Context-specific adaptation of the gain of the oculomotor response to lateral translation using roll and pitch head tilts as contexts. Exp Brain Res 146, 388–393, 2002.
749. Shelhamer M, Ravina B, Kramer PD. Adaptation of the gain of the angular vestibulo-ocular reflex when retinal slip is zero. Soc Neurosci Abstr 21, 518, 1995.
750. Shelhamer M, Roberts DC, Zee DS. Dynamics of the human linear vestibulo-ocular reflex at medium frequency and modification by short-term training. J Vestib Res 10, 271–282, 2000.
751. Shelhamer M, Robinson DA, Tan HS. Context-specific adaptation of the gain of the vestibulo-ocular reflex in humans. J Vestib Res 2, 89–96, 1992.
752. Shelhamer M, Young LR. The interaction of otolith organ stimulation and smooth pursuit tracking. J Vestib Res 4, 1–15, 1994.
753. Shelhamer M, Zee DS. Context-specific adaptation and its significance for neurovestibular problems of space flight. J Vestib Res 13, 345–362, 2003.
754. Sherman KR, Keller EL. Vestibulo-ocular reflexes of adventitiously and congenitally blind adults. Invest Ophthalmol Vis Sci 27, 1154–1159, 1986.
755. Shinder ME, Purcell IM, Kaufman GD, Perachio AA. Vestibular efferent neurons project to the flocculus. Brain Res 889, 288–294, 2001.
756. Shupert C, Fuchs AF. Development of conjugate human eye movements. Vision Res 28, 585–596, 1988.
757. Simons B, Büttner U. The influence of age on optokinetic nystagmus. Eur Arch Psychiatry Neurol Sci 234, 369–373, 1986.
758. Skavenski AA, Robinson DA. Role of abducens neurons in vestibuloocular reflex. J Neurophysiol 36, 724–738, 1973.
759. Smith HL, Galiana HL. The role of structural symmetry in linearizing ocular reflexes. Biol Cybern 65, 11–22, 1991.
760. Smith MR, Nelson AB, Du Lac S. Regulation of firing response gain by calcium-dependent mechanisms in vestibular nucleus neurons. J Neurophysiol 87, 2031–2042, 2002.
761. Smith PF. Pharmacology of the vestibular system. Curr Opin Neurol 13, 31–37, 2000.
762. Smith PF, Curthoys IS. Mechanisms of recovery following unilateral labyrinthectomy: a review. Brain Res Rev 14, 155–180, 1989.
763. Smith PF, Darlington CL. Can vestibular compensation be enhanced by drug treatment? A review of recent evidence. J Vestib Res 4, 169–180, 1994.
764. Smith PF, Zheng Y, Paterson S, Darlington CL. The contribution of nitric oxide to vestibular compensation: are there species differences? Acta Otolaryngol. Suppl 545, 57–60, 2001.
765. Smith R. Vergence eye-movement response to whole-body linear acceleration stimuli in man. Ophthal Physiol Opt 5, 303–311, 1985.
766. Snyder LH, King WM. Behavior and physiology of the macaque vestibulo-ocular reflex response to sudden off-axis rotation: computing eye translation. Brain Res Bull 40, 293–301, 1996.
767. Snyder LH, King WM. The effect of viewing distance and the location of the axis of rotation on the monkey's vestibulo-ocular reflex (VOR). I. Eye movement responses. J Neurophysiol 67, 861–874, 1992.
768. Snyder LH, Lawrence DW, King WM. Changes in vestibulo-ocular reflex (VOR) anticipate changes in vergence angle in monkey. Vision Res 32, 569–575, 1992.
769. Solomon D, Cohen B. Stimulation of the nodulus and uvula discharges velocity storage in the vestibuloocular reflex. Exp Brain Res 102, 57–68, 1994.
770. Solomon D, Straumann D, Zee DS. Three-dimensional eye movement during vertical axis rotation: Effects of visual suppression, orbital eye position and head position. In Fetter M, Haslwanter T, Misslisch H, Tweed D (eds). Three-dimensional Kinematics of Eye, Head and Limb Movement. Harwood Academic Publishers, Amsterdam,1997, pp 197–208.
771. Solomon D, Zee DS, Straumann D. Torsional and horizontal vestibular ocular reflex adaptation: three-dimensional eye movement analysis. Exp Brain Res 152, 150–155, 2003.
771a. Sprenger A, Zils E, Stritzke G, Kruger A, Rambold H, Helmchen C. Do predictive mechanisms improve the angular vestibulo-ocular reflex in vestibular neuritis? Audiol Neurootol 11, 53–58, 2005.
772. Steinhausen W. Über die Beobachtung der Cupula in den Bogengängsampullen des Labyrinthes bei

des lebenden Hechts. Pflügers Archiv für die Gesante Physiologie des Meschen und der Tierre 232, 500–512, 1933.
773. Stewart CM, Mustari MJ, Perachio AA. Visual-vestibular interactions during vestibular compensation: role of the pretectal NOT in horizontal VOR recovery after hemilabyrinthectomy in rhesus monkey. J Neurophysiol 94, 2653–2666, 2005.
774. Stodieck SRG, Brandt T, Büttner U. Visual and vestibular epileptic seizures. Electroencephalogr Clin Neurophysiol 75, 65–66, 1990.
775. Straube A, Brandt T. Importance of the visual and vestibular cortex for self-motion perception in man (circularvection). Human Neurobiol 6, 211–218, 1987.
776. Strupp M, Arbusow V, Dieterich M, Sautier W, Brandt T. Perceptual and oculomotor effects of neck muscle vibration in vestibular neuritis—ipsilateral somatosensory substitution of vestibular function. Brain 121, 677–685, 1998.
777. Strupp M, Glasauer S, Schneider E, et al. Anterior canal failure: ocular torsion without perceptual tilt due to preserved otolith function. J Neurol Neurosurg Psychiatry 74, 1336–1338, 2003.
778. Suárez C, Diaz C, Tolivia J, et al. Morphometric analysis of the human vestibular nuclei. Anat Rec 247, 271–288, 1997.
779. Sugiuchi Y, Izawa Y, Ebata S, Shinoda Y. Vestibular cortical area in the periarcuate cortex: its afferent and efferent projections. Ann N Y Acad Sci 1039, 111–123, 2005.
780. Suzuki J-I, Tokumasu K, Goto K. Eye movements from single utricular nerve stimulation in the cat. Acta Otolaryngol (Stockh) 68, 350–362, 1969.
781. Suzuki M, Kitano H, Ito R, et al. Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. Brain Res Cogn Brain Res 12, 441–449, 2001.
782. Suzuki Y, Kase M, Kato H, Fukushima K. Stability of ocular counterrolling and Listing's plane during static roll-tilts. Invest Ophthalmol Vis Sci 38, 2103–2111, 1997.
783. Szentágothai J. The elementary vestibuloocular reflex. J Neurophysiol 13, 395–407, 1950.
784. Tabak S, Collewijn H. Human vestibulo-ocular responses to rapid, helmet-driven head movements. Exp Brain Res 102, 367–378, 1994.
785. Tabak S, Collewijn H, Boumans LJJM. Deviation of the subjective vertical in long-standing unilateral vestibular loss. Acta Otolaryngol (Stockh) 117, 1–16, 1997.
786. Tabata H, Yamamoto K, Kawato M. Computational study on monkey VOR adaptation and smooth pursuit based on the parallel control-pathway theory. J Neurophysiol 87, 2176–2189, 2002.
787. Takagi A, Sando I, Takahashi H. Computer-aided three-dimensional reconstruction and measurement of semicircular canals and their cristae in man. Acta Otolaryngol (Stockh) 107, 362–365, 1989.
788. Takeda N, Igarashi M, Koizuka I, Chae S, Matsunaga T. Recovery of the otolith-ocular reflex after unilateral deafferentation of the otolith organs in squirrel monkeys. Acta Otolaryngol (Stockh) 110, 25–30, 1990.
789. Takemori S. Compensation after sudden loss of unilateral vestibular function and optokinetic afternystagmus. Acta Otolaryngol (Stockh) Suppl 528, 103–108, 1997.
790. Takemura A, Kawano K. Sensory-to-motor processing of the ocular-following response. Neurosci Res 43, 201–206, 2002.
791. Tang Y, Lopez I, Baloh RW. Age-related change of the neuronal number in the human medial vestibular nucleus: a stereological investigation. J Vestib Res 11, 357–363, 2001.
792. Telford L, Seidman SH, Paige GD. Canal-otolith interactions in the squirrel monkey vestibulo-ocular reflex and the influence of fixation distance. Exp Brain Res 118, 115–125, 1998.
793. Telford L, Seidman SH, Paige GD. Canal-otolith interactions driving vertical and horizontal eye movements in the squirrel monkey. Exp Brain Res 109, 407–418, 1996.
794. Telford L, Seidman SH, Paige GD. Dynamics of squirrel monkey linear vestibuloocular reflex and interactions with fixation distance. J Neurophysiol 78, 1775–1790, 1997.
795. Ter Braak JWG. Untersuchungen über optokinetischen nystagmus. Archives Neerlandaises de Physiologie de l'homme et des animaux 21, 309–376, 1936.
796. Thier P, Erickson RG. Vestibular inputs to visual-tracking neurons in area MST of awake rhesus monkeys. Ann N Y Acad Sci 656, 960–963, 1992.
797. Thomke F, Hopf HC. Pontine lesions mimicking acute peripheral vestibulopathy. J Neurol Neurosurg Psychiatry 66, 340–349, 1999.
798. Thurston SE, Leigh RJ, Abel LA, Dell'Osso LF. Hyperactive vestibuloocular reflex in cerebellar degeneration: pathogenesis and treatment. Neurology 37, 53–57, 1987.
799. Thurtell MJ, Black RA, Halmagyi GM, Curthoys IS, Aw ST. Vertical eye position-dependence of the human vestibuloocular reflex during passive and active yaw head rotations. J Neurophysiol 81, 2415–2428, 1999.
800. Tian J-R, Shubayev I, Demer JL. Impairments in the initial horizontal vestibulo-ocular reflex of older humans. Exp Brain Res 137, 309–322, 2001.
801. Tian J, Crane BT, Demer JL. Vestibular catch-up saccades in labyrinthine deficiency. Exp. Brain Res 131, 448–457, 2000.
802. Tian J, Zee DS, Walker MF. Eye-position dependence of torsional velocity during step-ramp pursuit and transient yaw rotation in humans. Exp Brain Res, published online, 2005.
803. Tian JR, Crane BT, Demer JL. Human surge linear vestibulo-ocular reflex during tertiary gaze viewing. Ann N Y Acad Sci 1039, 489–493, 2005.
804. Tian JR, Crane BT, Wiest G, Demer JL. Effect of aging on the human initial interaural linear vestibulo-ocular reflex. Exp Brain Res 145, 142–149, 2002.
805. Tian JR, Shubayev I, Baloh RW, Demer JL. Impairments in the initial horizontal vestibulo-ocular reflex of older humans. Exp Brain Res 137, 309–322, 2001.
806. Tian JR, Shubayev I, Demer JL. Dynamic visual acuity during transient and sinusoidal yaw rotation in normal and unilaterally vestibulopathic humans. Exp Brain Res 137, 12–25, 2001.
807. Tian J-R, Crane BT, Demer JL. Vestibular catch-up saccades in labyrinthine deficiency. Exp Brain Res 131, 448–457, 2000.

808. Tijssen MAJ, Straathof CSM, Hain TC, Zee DS. Optokinetic afternystagmus in humans: normal values of amplitude, time constant and asymmetry. Ann Otol Rhinol Laryngol 98, 741–746, 1989.
809. Tiliket C, Shelhamer M, Tan HS, Zee DS. Adaptation of the vestibulo-ocular reflex with the head in different orientations and positions relative to the axis of body rotation. J Vestib Res 3, 181–196, 1993.
810. Tilikete C, Rode G, Nighoghossian N, Boisson D, Vighetto A. Otolith manifestations in Wallenberg syndrome. Rev Neurol (Paris) 157, 198–208, 2001.
811. Tilikete C, Ventre-Domine J, Denise P, Nighoghossian N, Vighetto A. Otolith dysfunction in skew deviation after brain stem lesions. Abnormalities of eye movements induced by off-vertical-axis rotation (OVAR). J Vestib Res 10, 179–192, 2000.
812. Todd NP, Rosengren SM, Colebatch JG. A short latency vestibular evoked potential (VsEP) produced by bone-conducted acoustic stimulation. J Acoust Soc Am 114, 3264–3272, 2003.
813. Tomlinson RD, Cheung R, Blakeman A. Naso-occipital vestibulo-ocular reflex responses in normal subjects. IEEE Eng Med Biol Mag 19, 43–47, 2000.
814. Tomlinson RD, McConville KMV, Na E-Q. Behavior of cells without eye movement sensitivity in the vestibular nuclei during combined rotational and translational stimuli. J Vestib Res 6, 145–158, 1996.
815. Toupet M, Pialoux P. The perverted nystagmus. Ann Otolaryngol Chir Cervicofac 98, 319–338, 1981.
816. Trillenberg P, Shelhamer M, Roberts DC, Zee DS. Cross-axis adaptation of torsional components in the yaw-axis vestibulo-ocular reflex. Exp Brain Res 148, 158–165, 2003.
817. Trillenberg P, Zee DS, Shelhamer M. On the distribution of fast-phase intervals in optokinetic and vestibular nystagmus. Biol Cybern 87, 68–78, 2002.
818. Tusa RJ, Grant MP, Buettner U, Herdman S, Zee DS. Influence of head pitch on high-velocity horizontal VOR in normal subjects and patients with unilateral vestibular nerve section. Acta Otolaryngol (Stockh) 116, 507–512, 1998.
819. Tweed D, Fetter M, Sievering D, Misslisch H, Koenig E. Rotational kinematics of the human vestibuloocular reflex. II. Velocity steps. J Neurophysiol 72, 2480–2489, 1994.
820. Tweed D, Haslwanter T, Fetter M. Optimizing gaze control in three dimensions. Science 281, 1363–1366, 1998.
821. Tweed D, Fetter M, Sievering D, et al. Rotational kinematics of the human vestibuloocular reflex. I. Gain matrices. J Neurophysiol 72, 2467–2479, 1994.
822. Uchino Y. Otolith and semicircular canal inputs to single vestibular neurons in cats. Biol Sci Space 15, 375–381, 2001.
823. Uchino Y, Sasaki M, Sato H, Bai R, Kawamoto E. Otolith and canal integration on single vestibular neurons in cats. Exp Brain Res 64, 271–285, 2005.
824. Uchino Y, Sasaki M, Sato H, et al. Utriculoocular reflex arc of the cat. J Neurophysiol 76, 1896–1903, 1996.
825. Uchino Y, Sato H, Suwa H. Excitatory and inhibitory inputs from saccular afferents to single vestibular neurons in the cat. J Neurophysiol 78, 2186–2192, 1997.
826. Uchino Y, Sato H, Zakir M, et al. Commissural effects in the otolith system. Exp Brain Res 136, 421–430, 2001.
827. Uemura T, Cohen B. Effects of vestibular nuclei lesions on vestibulo-ocular reflexes and posture in monkeys. Acta Otolaryngol (Stockh) Suppl 315, 1–71, 1973.
828. Valmaggia C, Gottlob I. Optokinetic nystagmus elicited by filling-in in adults with central scotoma. Invest Ophthalmol Vis Sci 43, 1804–1808, 2002.
829. Valmaggia C, Proudlock F, Gottlob I. Optokinetic nystagmus in strabismus: are asymmetries related to binocularity? Invest Ophthalmol Vis Sci 44, 5142–5150, 2003.
830. van Alphen AM, De Zeeuw CI. Cerebellar LTD facilitates but is not essential for long-term adaptation of the vestibulo-ocular reflex. Eur J Neurosci 16, 486–490, 2002.
831. Van Den Berg AV, Collewijn H. Directional asymmetries of human optokinetic nystagmus. Exp Brain Res 70, 597–604, 1988.
832. Ventre-Dominey J, Nighoghossian N, Denise P. Evidence for interacting cortical control of vestibular function and spatial representation in man. Neuropsychologia 41, 1884–1898, 2003.
833. Ventre-Dominey J, Nighoghossian N, Denise P. Interaction between cortical control of vestibular function and spatial representation in man. Ann N Y Acad Sci 1039, 494–497, 2005.
834. Vibert D, Hausler R, Safran AB. Subjective visual vertical in peripheral unilateral vestibular diseases. J Vestib Res 9, 145–152, 1999.
835. Vidal PP, Vibert N, Serafin M, et al. Intrinsic physiological and pharmacological properties of central vestibular neurons. Adv Otorhinolaryngol 55, 26–81, 1999.
836. Viirre E, Tweed D, Milner K, Vilis T. A reexamination of the gain of the vestibuloocular reflex. J Neurophysiol 56, 439–450, 1986.
837. Viirre ES, Cadera W, Vilis T. Monocular adaptation of the saccadic system and vestibuloocular reflex. Invest Ophthalmol Vis Sci 29, 1339–1347, 1988.
838. Viirre ES, Demer JL. The human vertical vestibulo-ocular reflex during combined linear and angular acceleration with near-target fixation. Exp Brain Res 112, 313–324, 1996.
839. Vilis T, Tweed D. A matrix analysis for a conjugate vestibulo-ocular reflex. Biol Cybern 59, 237–245, 1988.
840. Vitte E, Derosier C, Caritu Y, et al. Activation of the hippocampal formation by vestibular stimulation: a functional magnetic resonance imaging study. Exp Brain Res 112, 523–526, 1996.
841. Voogd J, Gerrits NM, Ruigrok NM. Organization of the vestibulo-cerebellum. In Highstein S, Cohen B, Büttner-Ennever JA (eds). New Directions in Vestibular Research. The New York Academy of Sciences, New York,1996, pp 553–579.
842. Voogd J, Wylie DR. Functional and anatomical organization of floccular zones: a preserved feature in vertebrates. J Comp Neurol 470, 107–112, 2004.
843. Wade NJ, Swanston MT, Howard IP, Ono H, Shen X. Induced rotary motion and ocular torsion. Vision Res 31, 1979–1983, 1991.
844. Wade SW, Curthoys IS. The effect of ocular torsional

position on perception of the roll-tilt of visual stimuli. Vision Res 37, 1071–1078, 1997.
845. Waespe W, Cohen B, Raphan T. Role of the flocculus and paraflocculus in optokinetic nystagmus and visual-vestibular interactions: effects of lesions. Exp Brain Res 50, 9–33, 1983.
846. Waespe W, Cohen B, Raphan T. Dynamic modification of the vestibulo-ocular reflex by nodulus and uvula. Science 228, 199–202, 1985.
847. Waespe W, Henn V. Vestibular nuclei activity during optokinetic after-nystagmus (OKAN) in the alert monkey. Exp Brain Res 30, 323–330, 1977.
848. Waespe W, Henn V. Neuronal activity in the vestibular nuclei of the alert monkey during vestibular and optokinetic stimulation. Exp Brain Res 27, 523–538, 1977.
849. Waespe W, Schwartz U. Characteristics of eye velocity storage during periods of suppression and reversal of eye velocity in monkeys. Exp Brain Res 65, 49–58, 1986.
850. Walker MF, Shelhamer M, Zee DS. Eye-position dependence of torsional velocity during interaural translation, horizontal pursuit, and yaw-axis rotation in humans. Vision Res 44, 613–620, 2004.
851. Walker MF, Zee DS. Rectified cross-axis adaptation of the vestibulo-ocular reflex in rhesus monkey. Ann N Y Acad Sci 956, 543–545, 2002.
852. Walker MF, Zee DS. Cerebellar disease alters the axis of the high-acceleration vestibulo-ocular reflex. J Neurophysiol 94, 3417–3429, 2005.
853. Walker MF, Zee DS. Directional abnormalities of vestibular and optokinetic responses in cerebellar disease. Ann N Y Acad Sci 871, 205–220, 1999.
854. Walker MF, Zee DS. Asymmetry of the pitch vestibulo-ocular reflex in patients with cerebellar disease. Ann N Y Acad Sci 1039, 349–358, 2005.
855. Wall C III, Furman JMR. Eyes open versus eyes closed: effects on human rotational responses. Acta Otolaryngol (Stockh) 98, 548–550, 1989.
856. Wall C III, Furman JMR. Nystagmus responses in a group of normal humans during earth-horizontal axis rotation. Acta Otolaryngol (Stockh) 108, 327–335, 1989.
857. Wall C III, Smith TR, Furman JM. Plasticity of the human otolith-ocular reflex. Acta Otolaryngol (Stockh) 112, 413–420, 1992.
858. Wallman J. Subcortical optokinetic mechanisms. In Miles FA, Wallman J (eds). Visual Motion and its Role in the Stabilization of Gaze. Elsevier, Amsterdam,1993, pp 321–342.
859. Wang L, Soderberg PG, Tengroth B. Influence of target direction, luminance and velocity on monocular horizontal optokinetic nystagmus. Acta Ophthalmologica 71, 578–585, 1993.
860. Washio N, Suzuki Y, Sawa M, Ohtsuka K. Gain of human torsional optokinetic nystagmus depends on horizontal disparity. Invest Ophthalmol Vis Sci 46, 133–136, 2005.
861. Watson P, Barber HO, Deck J, Terbrugge, K. Positional vertigo and nystagmus of central origin. Can J Neurol Sci 8, 133–137, 1981.
862. Wearne S, Raphan T, Cohen B. Control of spatial orientation of the angular vestibuloocular reflex by the nodulus and uvula. J Neurophysiol 79, 2690–2715, 1998.
863. Wearne S, Raphan T, Cohen B. Contribution of vestibular commissural pathways to spatial orientation of the angular vestibuloocular reflex. J Neurophysiol 78, 1193–1197, 1997.
864. Wearne S, Raphan T, Cohen B. Nodulo-uvular control of central vestibular dynamics determines spatial orientation of the angular vestibulo-ocular reflex. Ann N Y Acad Sci 781, 364–384, 1996.
865. Wearne S, Raphan T, Waespe W, Cohen B. Control of the three-dimensional dynamic characteristics of the angular vestibulo-ocular reflex by the nodulus and uvula. Progr Brain Res 114, 321–334, 1997.
866. Weber KD, Fletcher WA, Melvill JG, Block EW. Podokinetic after-rotation in patients with compensated unilateral vestibular ablation. Exp Brain Res 147, 554–557, 2002.
867. Wei G, Lafortune SH, Ireland DJ, Jell RM. Modification of vertical OKN and vertical OKAN asymmetry in humans during parabolic flight. J Vestib Res 7, 21–34, 1997.
868. Wei G, Lafortune SH, Ireland DJ, Jell RM. Human vertical optokinetic nystagmus and after-response, and their dependence upon head orientation with respect to gravity. J Vestib Res 4, 37–47, 1994.
869. Wei M, Angelaki DE. Cross-axis adaptation of the translational vestibulo-ocular reflex. Exp Brain Res 138, 304–312, 2001.
870. Wei M, DeAngelis GC, Angelaki DE. Do visual cues contribute to the neural estimate of viewing distance used by the oculomotor system? J Neurosci 23, 8340–8350, 2003.
871. Weissenstein L, Ratnam R, Anastasio TJ. Vestibular compensation in the horizontal vestibulo-ocular reflex of the goldfish. Behav Brain Sci 75, 127–137, 1996.
872. Weissman BM, DiScenna AO, Ekelman BL, Leigh RJ. The effect of eyelid closure and vocalization upon the vestibuloocular reflex during rotational testing. Ann Otol Rhinol Laryngol 95, 548–550, 1989.
873. Weissman BM, DiScenna AO, Leigh RJ. Maturation of the vestibuloocular reflex in normal infants during the first 2 months of life. Neurology 39, 534–538, 1989.
874. Welgampola MS, Colebatch JG. Characteristics and clinical applications of vestibular-evoked myogenic potentials. Neurology 64, 1682–1688, 2005.
875. Welgampola MS, Rosengren SM, Halmagyi GM, Colebatch JG. Vestibular activation by bone conducted sound. J Neurol Neurosurg Psychiatry 74, 771–778, 2003.
876. Wende S, Nakayama N, Schwerdtfeger P. The internal auditory artery: (embryology, anatomy, angiography, pathology). J Neurol 210, 21–31, 1975.
877. Wiest G, Demer JL, Tian J, Crane BT, Baloh RW. Vestibular function in severe bilateral vestibulopathy. J Neurol Neurosurg Psychiatry 71, 53–57, 2001.
878. Wiest G, Zimprich F, Prayer D, et al. Vestibular processing in human paramedian precuneus as shown by electrical cortical stimulation. Neurology 62, 473–475, 2004.
879. Wilson VJ, Melvill Jones G. Mammalian Vestibular Physiology. Plenum Press, New York, 1979.
880. Wong AM, Sharpe JA, Tweed D. The vestibulo-ocular reflex in fourth nerve palsy: deficits and adaptation. Vision Res. 42, 2205–2218, 2002.
881. Wong AM, Tweed D, Sharpe JA. Adaptations and deficits in the vestibulo-ocular reflex after sixth nerve palsy. Invest Ophthalmol Vis Sci 43, 99–111, 2002.
882. Yagi T, Ohyama Y, Suzuki K, Kamura E, Kokawa T. 3D analysis of nystagmus in peripheral vertigo. Acta Otolaryngol (Stockh) 117, 135–138, 1997.
883. Yagi T, Shimizu M, Sekine S, Kamio T. New neurootological test for detecting cerebellar dysfunction. Vestibulo-ocular reflex changes with horizontal vision-reversal prisms. Ann Otorhinolaryngol 90, 276–280, 1981.
884. Yakushin SB, Bukharina SE, Raphan T, Buttner-Ennever J, Cohen B. Adaptive changes in the angular VOR: duration of gain changes and lack of effect of nodulo-uvulectomy. Ann N Y Acad Sci 1004, 78–93, 2003.
885. Yakushin SB, Dai M, Raphan T, et al. Changes in the vestibulo-ocular reflex after plugging of the semicircular canals. Ann N Y Acad Sci 942, 287–299, 2001.
886. Yakushin SB, Raphan T, Cohen B. Gravity-specific adaptation of the angular vestibuloocular reflex: dependence on head orientation with regard to gravity. J Neurophysiol 89, 571–586, 2003.
887. Yakushin SB, Reisine H, Buttner-Ennever J, Raphan T, Cohen B. Functions of the nucleus of the optic tract (NOT). I. Adaptation of the gain of the horizontal vestibulo-ocular reflex. Exp Brain Res 131, 416–432, 2000.
888. Yakushin SB, Xiang Y, Raphan T, Cohen B. Spatial distribution of gravity dependent gain changes in the vestibulo-ocular reflex. J Neurophysiol 93, 3693–3698, 2005.
889. Yakushin SB, Xiang Y, Raphan T, Cohen B. The role of gravity in adaptation of the vertical angular vestibulo-ocular reflex. Ann N Y Acad Sci 1039, 97–110, 2005.
890. Yamamoto K, Takemura A, Kawano K, Kawato M. A computational simulation of the adaptation of ocular following responses. Soc Neurosci Abstr 24, 1405, 1998.
891. Yen MT, Herdman SJ, Tusa RJ. Oscillopsia and pseudonystagmus in kidney transplant patients. Am J Ophthalmol 128, 768–770, 1999.
892. Young LR. Models for neurovestibular adaptation. J Vestib Res 13, 297–307, 2003.
893. Zasorin NL, Baloh RW, Myers LB. Acetazolamide-responsive episodic ataxia syndrome. Neurology 33, 1212–1214, 1983.
894. Zee DS. Considerations on the mechanisms of alternating skew deviation in patients with cerebellar lesions. J Vestib Res 6, 395–401, 1996.
895. Zee DS. Ophthalmoscopy in examination of patients with vestibular disorders. Ann Neurol 3, 373–374, 1978.
896. Zee DS. The organization of the brainstem ocular motor subnuclei. Ann Neurol 4, 384–385, 1978.
897. Zee DS, Fetter M, Proctor L. Recovery from unilateral labyrnthectomy in primate: Effects of usual inputs and considerations upon Ewald's second law. In Huang JC, Daunton NGWVJ (eds). Basic and Applied Aspects of Vestibular Function. University of Hong Kong Press, Hong Kong, 1988, pp 125–132.
898. Zee DS, Friendlich AR, Robinson DA. The mechanism of downbeat nystagmus. Arch Neurol 30, 227–237, 1974.
899. Zee DS, Preziosi TJ, Proctor LR. Bechterew's phenomenon in a human. Ann Neurol 12, 495–496, 1982.
900. Zee DS, Tusa R, Herdman S, Butler P, Gücer G. Effects of occipital lobectomy upon eye movements in primate. J Neurophysiol 58, 883–907, 1987.
901. Zee DS, Walker MF, Ramat S. The cerebellar contribution to eye movements based upon lesions: binocular three-axis control and the translational vestibulo-ocular reflex. Ann N Y Acad Sci 956, 178–189, 2002.
902. Zee DS, Walker MF. In Chalupa LM, Werner JS (eds). Cerebellar Control of Eye Movements in the Visual Neurosciences. MIT Press, Cambridge, MA, 2003, pp 1485–1498.
903. Zee DS, Yamazaki A, Butler PH, Gücer G. Effects of ablation of the flocculus and paraflocculus on eye movements in primate. J Neurophysiol 46, 878–899, 1981.
904. Zee DS, Yee RD, Robinson DA. Optokinetic responses in labyrinthine-defective human beings. Brain Res 113, 423–428, 1976.
905. Zhang R, Ashton J, Horii A, Darlington CL, Smith PF. Immunocytochemical and stereological analysis of GABA(B) receptor subunit expression in the rat vestibular nucleus following unilateral vestibular deafferentation. Brain Res 1037, 107–113, 2005.
906. Zhang X, et al. Convergence of the anterior semicircular canal and otolith afferents on cat single vestibular neurons. Exp Brain Res 147, 407–417, 2002.
907. Zhang X, Zakir M, Meng H, Sato H, Uchino Y. Convergence of the horizontal semicircular canal and otolith afferents on cat single vestibular neurons. Exp Brain Res 140, 1–11, 2001.
908. Zhou G, Cox LC. Vestibular evoked myogenic potentials: history and overview. Am J Audiol 13, 135–143, 2004.
909. Zhou W, Weldon P, Tang B, King WM. Rapid motor learning in the translational vestibulo-ocular reflex. J Neurosci 23, 4288–4298, 2003.
910. Zupan LH, Merfeld DM. Neural processing of gravito-inertial cues in humans. IV. Influence of visual rotational cues during roll optokinetic stimuli. J Neurophysiol 89, 390–400, 2003.
911. Zupan LH, Merfeld DM, Darlot C. Using sensory weighting to model the influence of canal, otolith and visual cues on spatial orientation and eye movements. Biol Cybern 86, 209–230, 2002.
912. Zupan LH, Peterka RJ, Merfeld DM. Neural processing of gravito-inertial cues in humans. I. Influence of the semicircular canals following post-rotatory tilt. J Neurophysiol 84, 2001–2015, 2000.