

Chapter 2

Physiology of central pathways

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Abstract

The relative simplicity of the neural circuits that mediate vestibular reflexes is well suited for linking systems and cellular levels of analyses. Notably, a distinctive feature of the vestibular system is that neurons at the first central stage of sensory processing in the vestibular nuclei are premotor neurons; the same neurons that receive vestibular-nerve input also send direct projections to motor pathways. For example, the simplicity of the three-neuron pathway that mediates the vestibulo-ocular reflex leads to the generation of compensatory eye movements within ~5 ms of a head movement. Similarly, relatively direct pathways between the labyrinth and spinal cord control vestibulospinal reflexes. A second distinctive feature of the vestibular system is that the first stage of central processing is strongly multimodal. This is because the vestibular nuclei receive inputs from a wide range of cortical, cerebellar, and other brainstem structures in addition to direct inputs from the vestibular nerve. Recent studies in alert animals have established how extravestibular signals shape these “simple” reflexes to meet the needs of current behavioral goal. Moreover, multimodal interactions at higher levels, such as the vestibular cerebellum, thalamus, and cortex, play a vital role in ensuring accurate self-motion and spatial orientation perception.

INTRODUCTION

Electrophysiologic studies have provided fundamental insights into the functional circuitry of central vestibular pathways. Notably, the vestibular system differs from other sensory systems in that the same neurons that receive direct (i.e., monosynaptic) afferent input can also send direct projections to motoneurons. For example, the most direct pathway mediating the vestibulo-ocular reflex (VOR) pathway is mediated by a three-neuron pathway linking the vestibular afferents and eye muscle motoneurons through the vestibular nuclei. Likewise, a three-neuron pathway connecting vestibular afferents and spinal motoneurons contributes to vestibulospinal reflexes (VSRs). A second distinctive feature of the vestibular system is that the first stage of central processing is remarkably multimodal, as a result of the input it receives from numerous areas within the brainstem, as well as from the cerebellum and cortex (Fig. 2.1). These extravestibular signal inputs relay both sensory (i.e., cutaneous somatosensory, proprioceptive, and visual)

and motor-related information to the vestibular nuclei. As a result, vestibular reflex pathways are modulated in a behaviorally dependent manner in everyday life. In addition, this integration of vestibular and extravestibular cues is vital for cognitive functions such as perception of self-movement and spatial orientation. Recent single-unit studies in nonhuman primates have provided further insight into how the computations performed by the cerebellum and cortex shape the higher-level processing required for perception of self-movement and spatial orientation. The findings from these basic neurophysiologic studies have important implications for understanding the deficits observed clinically in patients.

THE VESTIBULAR NUCLEI: NEURAL CODING OF EXTERNALLY APPLIED MOTION

At the first stage of central processing, the vestibular complex comprises four main subdivisions: the medial, superior, lateral, and inferior (or descending) vestibular

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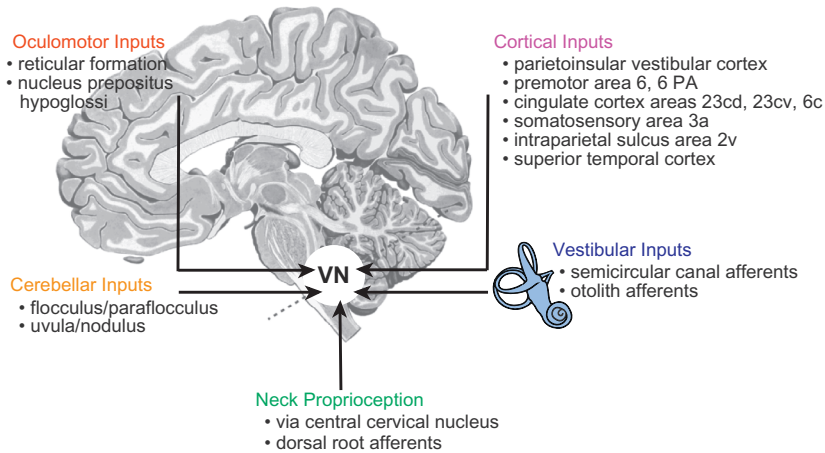


Fig. 2.1. The vestibular nuclei (VN) receive inputs from multiple brain areas, in addition to direct projections from the vestibular afferents of the VIIIth nerve. The midline is denoted by the diagonal dashed line.

nuclei, as well as other minor subgroups including the y and e groups. Although there is no strict segregation of afferent input within the subdivisions of the vestibular nuclei, each subdivision differs in the relative densities of its afferent inputs. For example, the medial and superior nuclei receive mostly horizontal and vertical semicircular canal input, respectively. In contrast, utricular and saccular afferents terminate mainly in the inferior and lateral vestibular nuclei.

General classification of cell types and linear systems analysis

Single-unit recording experiments in behaving monkeys have established how neurons in the vestibular nuclei encode applied rotations and translations. Neurons that respond to horizontal (yaw-axis) rotations are predominantly localized in the rostral medial vestibular nuclei and the ventrolateral vestibular nuclei (Fuchs and Kimm, 1975; Keller and Daniels, 1975; Chubb et al., 1984; Scudder and Fuchs, 1992; Cullen and McCrea, 1993). In contrast, neurons that respond to vertical (pitch- or roll-axis) rotations are primarily located in the superior and medial vestibular nuclei, as well as y-group (Tomlinson and Robinson, 1984; Partsalis et al., 1995; Dickman and Angelaki, 2004). Moreover, neurons that are sensitive to rotations can be further divided into three main classes based on their responses to passive whole-body rotations, translations, and voluntary eye movements. These include: (1) position-vestibular-pause (PVP) neurons; (2) vestibular-only (VO) neurons; and (3) eye-head (EH) neurons, which are each described in further detail below.

NEURONS THAT RESPOND TO ROTATIONAL HEAD MOTION

To date, most studies of vestibular processing have focused on characterizing neuronal responses to horizontal (yaw-axis) rotations, because they are logistically easier to apply in comparison to either pitch/roll rotations or translations. Vestibular nuclei neurons that respond to horizontal rotations are classified as type I or II neurons (Duensing and Schaefer, 1958), based on whether they are excited by ipsilaterally or contralaterally directed rotations, respectively. Prior studies in head-restrained alert monkeys have well described the responses of individual vestibular nuclei neurons that receive direct horizontal canal afferent input (reviewed in Cullen and Roy, 2004; Cullen, 2012). Notably, a significant percentage of type I PVP, VO, and EH can be activated at monosynaptic latencies by electric stimulation of the ipsilateral vestibular nerve (McCrea et al., 1987; Scudder and Fuchs, 1992). These type I neurons, which comprise the first stage of central processing in the vestibular system, are considered below in relation to their distinctive functional roles, specifically: (1) VOR neurons (i.e., PVP and EH neurons) and (2) posture/self-motion neurons (VO neurons).

VOR NEURONS

The angular VOR effectively stabilizes gaze during our daily activities by moving the eye in the opposite direction to the ongoing head rotation (Fig. 2.2A). The most direct pathway mediating this vital reflex comprises a three-neuron arc in which the semicircular canal afferents project to central neurons in the vestibular nuclei

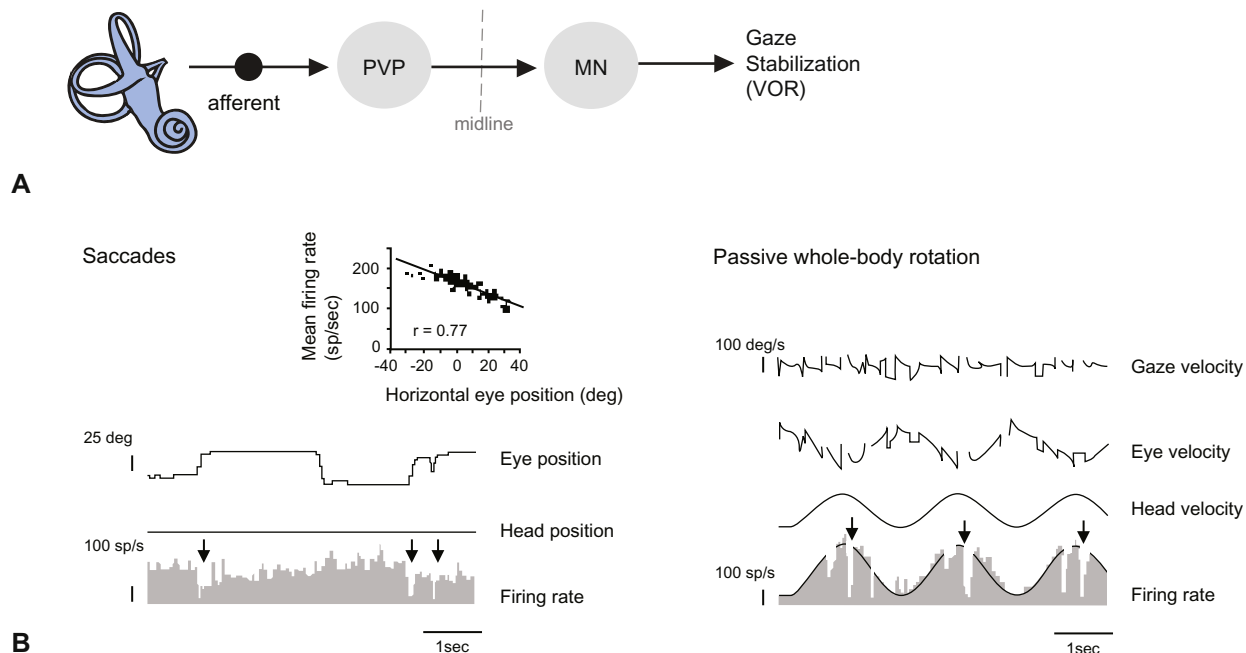


Fig. 2.2. Vestibular nuclei neurons mediate the vestibulo-ocular reflex (VOR). **(A)** Schematic diagram of the direct VOR pathway (top). Position-vestibular-pause (PVP) neurons constitute the middle link of this reflex; they receive direct afferent input and send strong inhibitory projections to ipsilateral abducens motoneurons (MN) to generate compensatory eye movements. **(B)** PVP neurons encode eye position during ocular fixation, head motion during whole-body rotation, and pause during saccades (arrows).

(i.e., VOR neurons), that in turn project to the extraocular motoneurons (Lorente de No, 1933). The majority of the neurons in the vestibular nuclei that comprise the middle link of the direct VOR pathway are type I PVP neurons (Fig. 2.2B). Note that the designation PVP is well established in the vestibular literature, and arose because these neurons carry specific signals during passive head rotations and eye movements. Specifically, the type I PVPs that comprise the direct VOR pathway: (1) carry signals related to contralateral eye position signals during visual fixation; (2) respond to vestibular input caused by ipsilateral head rotations; and (3) pause for saccadic eye movements. Additionally, indirect pathways through the vestibular cerebellum make important contributions to the VOR. In particular, there is a second class of neuron in the vestibular nuclei that receives direct projections from the floccular complex of the cerebellum as well as from the vestibular nerve (McFarland and Fuchs, 1992; Scudder and Fuchs, 1992; Cullen et al., 1993; Roy and Cullen, 2003; Lisberger et al., 1994a, b). These floccular target neurons generally respond to smooth-pursuit and visual cancellation of the VOR, in the same direction. Accordingly, they are also often called EH cells in the literature. EH neurons play a critical role in gaze stability by ensuring the VOR remains calibrated. This is because, as discussed below, EH neurons change their sensitivity to account for the effects of aging or

changes in environmental requirements (e.g., a new corrective lens prescription to correct myopia) to appropriately regulate the VOR response so that it remains accurate (for review, see Cullen, 2008).

POSTURE/SELF-MOTION NEURONS

The second category of vestibular nuclei neurons that receive direct afferent input are called VO neurons (Fig. 2.3A). Notably, VO neurons send projections to the spinal cord and are thought to contribute to the pathways that produce vestibular spinal reflexes (see review by Goldberg and Cullen, 2011). VO neurons are also reciprocally interconnected with the nodulus/uvula of the cerebellum (Reisine and Raphan, 1992), and this anatomic organization is an important component of the velocity storage mechanism that lengthens the time constant of the VOR beyond that provided by the afferent input. Finally, VO neurons provide vestibular input to vestibular-sensitive neurons in thalamus and cortex (Lang et al., 1979; Grusser et al., 1990). VO neurons respond to vestibular stimulation but not eye movements (Fig. 2.3B), and, unlike either PVP and EH neurons, do not project directly to eye motoneurons. Consequently, whereas PVPs and EHs mediate and calibrate the VOR to stabilize gaze and ensure clear vision in everyday life, VO neurons comprise the first stage of central processing

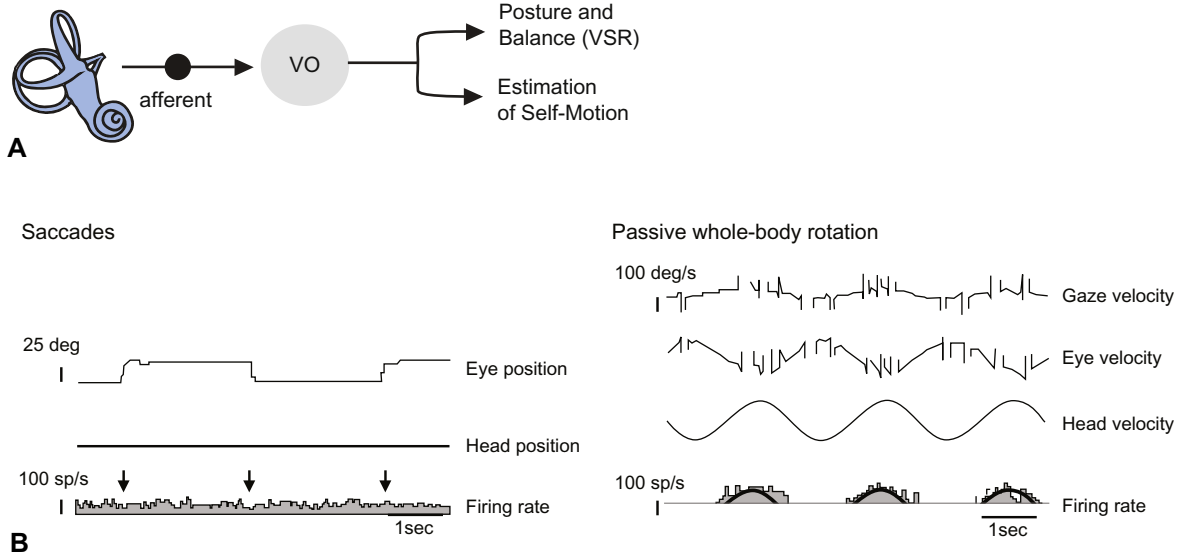


Fig. 2.3. Vestibular nuclei neurons mediate vestibulospinal reflexes and enable the accurate perception of self-motion and spatial orientation. **(A)** Schematic diagram of the contributions of vestibular-only (VO) neurons to vestibulospinal reflexes (VSR) and ascending pathways. VO neurons receive direct afferent input and send projections to spinal cord, cerebellum, and thalamus. **(B)** VO neurons are insensitive to eye position during ocular fixation or saccades, and robustly encode head motion during whole-body rotation (with comparable sensitivity in the dark and light).

in the vestibular pathways responsible for the reflexes underlying posture and balance, as well as the higher-order vestibular processing of head motion required for perception.

Traditionally, vestibular nuclei neuronal responses to sensory input have been characterized by estimating response gain and phase over several cycles of sinusoidal head rotation (reviewed in Cullen, 2012). This approach, termed linear systems analysis, has been applied to the vestibular system to understand how neurons encode head motion because it is commonly assumed that early vestibular processing is fundamentally linear. There are two main lines of evidence to provide support for this idea. First, numerous studies have shown that both afferents and their target neurons in the vestibular nuclei accurately encode the detailed time course of horizontal rotational head motion through linear changes in firing rate over a wide range of frequencies (reviewed in Goldberg, 2000; Cullen and Roy, 2004; Massot et al., 2011). In addition, *in vitro* studies have shown that central vestibular neurons linearly transduce synaptic inputs into changes in firing rate output (Bagnall et al., 2008; McElvain et al., 2015).

Indeed, in the last decade, the linear systems analysis approach has provided key insights into how early vestibular pathways encode rotational head motion over the physiologically relevant frequency range (Dickman and Angelaki, 2004; Sadeghi et al., 2007; Ramachandran and Lisberger, 2008; Massot et al., 2011). In particular,

the analysis of natural head motion has revealed significant power up to ~ 20 Hz (Huterer and Cullen, 2002; Carriot et al., 2014; Schneider et al., 2015). Accordingly, recent studies have characterized the responses of individual vestibular afferents and vestibular nuclei neurons by applying sinusoidal head rotations throughout this frequency range and computing response sensitivities and phases. Experiments using this approach have established that, in primates, both PVP neurons (Roy et al., 2003; Ramachandran and Lisberger, 2008) and VO neurons (Massot et al., 2011) respond with high-pass dynamics that are comparable to those of vestibular afferents. However, EH neurons show distinctive dynamics characterized by strikingly flat gain (and phase) tuning as a function of frequency (Ramachandran and Lisberger, 2008). To date, the functional implications of these differences are not yet fully understood; however, VOs show an increased phase lead relative to PVP neurons that is likely related to the higher inertia of the body versus head (Fernandez and Goldberg, 1971; Bilotto et al., 1982; Boyle et al., 1992).

NEURONS THAT RESPOND TO LINEAR HEAD MOTION: TRANSLATIONS AND TILT

In addition to receiving direct semicircular canal afferent input, the vestibular nuclei receive direct projections from otolith afferents. In fact, single neurons often receive convergent input such that they respond to

translational as well as rotational motion. Translation-sensitive neurons are categorized using the same nomenclature detailed above for rotationally sensitive neurons (i.e., PVP, EH, and VO neurons). In response to linear head motion, PVP and EH neurons in the vestibular nuclei mediate the translational VOR to produce compensatory eye movements that stabilize gaze. A direct disynaptic pathway exists between the otolith afferents and extraocular motoneurons (Uchino et al., 1994, 1996). However, the translational VOR, unlike the rotational VOR, is largely mediated by more complex polysynaptic pathways (Chen-Huang and McCrea, 1999; Meng et al., 2005; Meng and Angelaki, 2006). As a result, the latency of the translational VOR is relatively longer than that of the rotational VOR; compensatory eye movement generally lags head movement by more than 10 ms (Angelaki and McHenry, 1999) versus the short 5 ms delay of the rotational VOR (Huterer and Cullen, 2002).

VO neurons can also respond to both linear and rotational motion. The application of linear systems analysis has shown that, while the otolith afferent responses generally lead head linear acceleration, the responses of vestibular nuclei neuron fall into three categories: (1) “high-pass” neurons characterized by response modulation and phase leads that increase with frequency; (2) “flat” neurons characterized by constant response modulation and phase leads across frequency; and (3) “low-pass” neurons characterized by response modulation and phase leads that decrease with frequency (Angelaki and Dickman, 2000). In addition, individual vestibular nuclei neurons typically display broader directional tuning for linear motion than their otolith afferent input (Angelaki et al., 1992; Schor and Angelaki, 1992; Angelaki, 1993). Notably, the tuning of an individual otolith afferent is well described by a single preferred direction vector, and its sensitivity approaches zero for linear motion that is orthogonal to this preferred direction. This type of tuning in afferents is commonly referred to as one-dimensional tuning. In contrast, vestibular nuclei neurons display more complex tuning consistent with the fact that they typically receive converging otolith inputs that differ in preferred direction vector. As a result of this convergence, vestibular nuclei neurons typically respond to motion directed in either one or even two directions orthogonal to their preferred direction (Baker et al., 1984; Angelaki, 1992a, b; Yakushin et al., 1999, 2006; Chen-Huang and Peterson, 2006). This type of tuning is commonly referred to as two-dimensional or three-dimensional tuning, respectively (Angelaki and Dickman, 2000; Chen-Huang and Peterson, 2006). Thus, as a result of their convergence inputs, the dynamics of central otolith neuron responses are also more complex than those of peripheral otolith afferents.

Information transmission and detection thresholds in early vestibular pathways

A limitation of the linear system analyses approach traditionally applied to characterize vestibular afferent and central neuron responses is that it does not take into account the important role that neural variability can play in determining how the brain encodes sensory stimuli. Recently a series of studies have shown that semicircular canal afferents with more regular resting spike rates have lower sensitivities but transmit information (i.e., quantified in bits per second) about head rotations with higher fidelity as compared to afferents with more irregular resting spike rates (Sadeghi et al., 2007; Cullen, 2011, 2012; Massot et al., 2011; Neiman et al., 2011; Metzen et al., 2015). This then raises the question: how is information encoded by these two streams of afferent input combined at the next stage of processing?

To date, the available evidence suggests that inputs from both afferent classes are combined at the first stage of central processing in the vestibular nuclei – in VOR pathways (PVP and EH cells) as well as in vestibulospinal pathways (VO cells) (Highstein et al., 1987; Boyle et al., 1992). Recent experiments in the vestibular nuclei of monkeys have specifically provided insights about how neural variability constrains the information encoded by VO neurons (Massot et al., 2011). Somewhat surprisingly, although VO neurons typically have larger response gains than either regular or irregular afferents, they transmit less information over the physiologically relevant frequency range. Correspondingly, due to their high variability, VO neurons also demonstrate significantly higher rotation detection thresholds than even the relatively “noisy” irregular afferents. Overall, the lowest measured thresholds ($8^\circ/\text{s}$) are more than an order of magnitude larger than the perceptual thresholds measured in human studies ($0.5^\circ/\text{s}$). Indeed, it is only by combining the responses of many VO neurons (i.e., >20) that neuronal detection thresholds approach values measured during behavioral experiments (~ 2.5 vs. $0.5\text{--}1^\circ/\text{s}$; Clark, 1967; Guedry, 1974; Grabherr et al., 2008; Valko et al., 2012). It has been proposed that the activities of multiple VO neuron are combined at higher stages of processing to obtain the velocity detection thresholds measured in psychophysical experiments (Massot et al., 2011). In order to understand how vestibular pathways encode self-motion, it is necessary to not only characterize individual neurons, but also determine how information from individual neurons is combined. In particular, if fluctuations in neuronal responses are independent, neural noise will be averaged away when inputs are combined downstream (Averbeck and Lee, 2006) to compute the estimates of self-motion required for stable perception and accurate behavior in everyday life.

It is also interesting to note that the markedly higher variability displayed by vestibular central neurons could potentially serve to prevent phase locking or entrainment (Stein et al., 2005; Schneider et al., 2011). This approach may be common across sensory systems. For example, neurons in early visual pathways can transmit detailed information in their spike trains (Meister et al., 1995; Berry et al., 1997; Reich et al., 1997; Desbordes et al., 2008). In contrast, the spike trains of neurons in visual cortex appear to be characterized by relatively large variability (e.g., London et al., 2010). A point worth emphasizing is that a critical assumption of these prior analyses of vestibular processing is that a neuron's ability to reconstruct the stimulus (i.e., coding fraction) can be measured by computing the coding fraction (Gabbiani et al., 1996; Rieke et al., 1996). However, it has been recently shown that central vestibular neurons nonlinearly integrate their afferent input in a way that effectively both extends their coding range for head motion and preferentially encodes the high-frequency features of self-motion (Massot et al., 2012). This finding invalidates the commonly held assumption that the vestibular system uses a linear rate code to transmit information. Accordingly, experiments directed toward understanding the implication of nonlinear behaviors including phase locking and other spike timing codes will likely provide new insights into how self-motion information is encoded by these vestibular nuclei neurons for the subsequent computation of self-motion as well as gaze and posture control.

Vestibular nuclei: integration of canal and otolith afferent inputs

The activities that we engage in during our everyday lives (walking, running, riding in a vehicle) are characterized by complex multidimensional motion patterns that simultaneously stimulate the semicircular canal and otolith organs (Carriot et al., 2013; Schneider et al., 2015). For this reason, understanding how single neurons integrate the incoming information from both types of end organs is fundamental to furthering our knowledge of how the vestibular system encodes self-motion in everyday life. Projections from semicircular canal and otolith organ afferents show considerable overlap in the vestibular nuclei (Gacek, 1969; Dickman and Fang, 1996; Birinyi et al., 2001). However, individual vestibular nuclei neurons generally only receive input from a single semicircular canal and/or otolith organ (Straka and Dieringer, 2004). Interestingly, rotational and linear motion inputs combine in a spatially specific manner, either combining horizontal semicircular canal and utricular signals or vertical semicircular canal and saccular otolith signals (Straka et al., 2002).

Single-unit recording studies in the vestibular nuclei of primates have provided insight into the specific computations that are performed in early vestibular processing to integrate canal and otolith afferent inputs (Tomlinson et al., 1996; Siebold et al., 1999, 2001; Angelaki et al., 2004; Yakushin et al., 2006; Carriot et al., 2015). The majority of vestibular neurons receive convergent inputs, and numerous studies have focused on understanding how the brain integrates these inputs to discriminate tilt from translation. Specifically, while tilt activates both otolith and semicircular canal organs, translation activates only the otolith end organs. Thus, by integrating canal and otolith signals it is theoretically possible to discriminate tilt from translation. Indeed, many neurons in the vestibular nuclei preferentially encode translational motion such that they are relatively insensitive to changes in head orientation relative to gravity (reviewed in Angelaki and Cullen, 2008; Angelaki and Yakusheva, 2009). It has further been shown that inactivation of the semicircular canals can completely eliminate the presence of translation-coding cells (Shaikh et al., 2005; Yakusheva et al., 2007). Thus, interactions between otolith and canal signals allow neurons to selectively encode translational motion and remain relatively insensitive to changes in head orientation relative to gravity. Taken together, these results provide insight into how subjects discriminate tilt from translation (Glasauer and Merfeld, 1997; Angelaki et al., 1999; Merfeld et al., 1999; Bos and Bles, 2002; Zupan et al., 2002; Green and Angelaki, 2003, 2004; Laurens and Angelaki, 2011).

During common everyday activities, the otoliths and semicircular canals are both simultaneously and dynamically stimulated. However, in most prior studies the responses of vestibular nuclei neurons were independently characterized during pure rotations and pure translations. The few studies that have characterized neurons during more complex combined movement found that semicircular canal and otolith inputs are not summed linearly (Dickman and Angelaki, 2002; McArthur et al., 2011; Carriot et al., 2015). Instead vestibular nuclei neurons subadditively integrate semicircular canal and otolith inputs (Carriot et al., 2015), such that they show less modulation than that predicted by the addition of their responses to translation and rotations when each is applied alone. A potential benefit of this subadditive integration is that it effectively expands the dynamic linear range of vestibular neurons to prevent firing-rate saturation or cutoff (i.e., the cessation of firing) in response to high-amplitude natural head movements (Carriot et al., 2014; Schneider et al., 2015). Moreover, on average, the weighting of rotational sensitivities decreases with increasing frequency, whereas the translational weights increases with increasing frequency. This

frequency dependency provides a neural correlate for the finding in human psychophysical experiments that subjects more accurately perceive angular than linear displacement at lower frequencies (Ivanenko et al., 1997; MacNeilage et al., 2010).

Vestibular nuclei: multimodal integration

In everyday life, our sense of self-motion involves the integration of vestibular and extravestibular cues, including visual and proprioceptive sensory signals as well as information derived from our own motor commands. For example, when walking down the street, the visual system provides retinal-image motion (optic flow) cues, whereas the proprioceptive sensors of our muscles, tendons, and joints sense the relative position of neighboring parts of the body. In addition, information related to the motor commands that control our walking can theoretically contribute to the brain's estimate of self-motion. Recent single-unit recording experiments have revealed how single neurons in the vestibular nuclei integrate vestibular and extravestibular cues.

THE INTEGRATION OF VESTIBULAR AND VISUAL CUES

As we move through our environment, patterns in the apparent motion of objects, surfaces, and edges in a visual scene are produced by the relative motion between us and the world. The visual cues provided by this large-field visual motion induce reflexive eye movements to maintain stable gaze relative to visual space (Waespe and Henn, 1977a, b, 1979; Boyle et al., 1985). These compensatory eye movements are termed the optokinetic reflex (OKR). The OKR works synergistically with the VOR to maintain gaze stability, and is characterized by an initial rapid rise in eye velocity within ~ 100 ms of the start of visual motion followed by a slower build-up of eye velocity in primates. The initial rise is controlled by cortical inputs to OKR pathways, while the slower build-up is largely produced by a subcortical pathway that includes the nucleus of the optic tract (NOT) and the accessory optic system (AOS). Interestingly, the relative importance of brainstem and cortical inputs to the OKN pathways is species-dependent. Animals such as mice, gerbils, and rabbits show significant temporal-nasal asymmetries in their OKN responses (Collewyn, 1981; Kaufman, 2002; Stahl et al., 2006), while responses are symmetric in humans and monkeys. It has been proposed that cortical inputs to NOT neurons provide symmetric OKR responses of each eye, thereby ensuring stable binocular vision in primates (see discussion in Leigh and Zee, 2004). There is evidence to support this view. For example, OKN responses are asymmetric in human infants, whose pathways to cortical visual areas are not fully developed (Atkinson et al.,

1974; Schor, 1983) and in monkeys with lesions of the occipital cortex.

Neurons within the vestibular nuclei can simultaneously process visual and vestibular inputs – a finding that helps to explain why full-field motion on the retina not only provides an observer with an indication of how fast, and in what direction, the visual world is moving, but also leads to the sensation of self-rotation. Specifically, single-unit recording studies in the vestibular nuclei have indicated that eye movement-sensitive neurons (e.g., PVP neurons) show robust modulation during OKR (reviewed in Cullen, 2011, 2012). Thus, the same neurons play a major role in the premotor control of OKR eye movements as well as the VOR. It is also noteworthy that early studies concluded that all vestibular nuclei neuron classes are driven by optokinetic as well as vestibular stimulation (Waespe and Henn, 1977a, b; Büttner and Büttner, 1979; Boyle et al., 1985; Reisine and Raphan, 1992). However, the more complete quantitative analysis performed in recent studies has established that this is not the case. Specifically, VO neurons, unlike eye movement-sensitive neurons, do not show robust modulation during large-field visual stimulation either in mouse or primates (Beraneck and Cullen, 2007; Bryan and Angelaki, 2009). The same vestibular nuclei neurons that command OKR eye movements likely also contribute to an integrated “velocity storage” network that uses visual information to supplement the decaying signal from vestibular afferents during sustained head movements to encode self-motion (Cohen et al., 1983; Angelaki and Hess, 1995; Wearne et al., 1998).

THE INTEGRATION OF VESTIBULAR AND PROPRIOCEPTIVE CUES

There are marked differences in how vestibular and proprioceptive information is integrated across species. For example, both eye-sensitive and VO vestibular nuclei neurons can robustly respond to both proprioceptive as well as vestibular stimulation in mice, rats, cats, and alert squirrel monkeys (Boyle and Pompeiano, 1981; Anastasopoulos and Mergner, 1982; Wilson et al., 1990; Gdowski et al., 2001; Barresi et al., 2013; Medrea and Cullen, 2013). In these species, a given neuron's responses to combined stimulation are well approximated by the linear sum of its responses to vestibular and proprioceptive stimulation when each modality is activated in isolation. In contrast, proprioceptive responses are less pronounced in cynomolgus monkeys (Sadeghi et al., 2009) and are actually absent in rhesus monkeys (Roy and Cullen, 2001, 2004). It has been proposed, that these differences evolved as a result of variations in species-specific adaptations in gaze strategies during exploratory behavior. For example, cynomolgus and

rhesus monkeys commonly explore their environment with voluntary head-on-body movements termed gaze shifts (Freedman and Sparks, 1997, 2000; Goossens and van Opstal, 1997; McCluskey and Cullen, 2007). In contrast, head and body motion is more closely linked in rodents to enhance the efficacy of mechanisms that support the stabilization of the head relative to the body (e.g., Baker, 2005; Takemura and King, 2005). Thus, strong convergence with proprioceptive inputs in early vestibular pathways could be disadvantageous in monkeys (and presumably humans), which more commonly exercise voluntary control over the neck musculature.

THE INTEGRATION OF VESTIBULAR AND MOTOR-RELATED INFORMATION

As mentioned above, information related to the motor commands that produce active self-motion can also theoretically contribute to the brain's estimate of self-motion. Consistent with this idea, recent single-unit recording studies in alert-behaving primates have established that the efficacy of the pathways that mediate VOR as well as VSR is modulated in a behaviorally dependent manner during voluntary movements (Cullen, 2011, 2012). Notably, the head motion sensitivity of the vestibular nuclei neurons that mediate the VOR (i.e., PVP neurons) is substantially attenuated when the goal of the ongoing motor behavior is to voluntarily redirect (rather than stabilize) gaze. Likewise, the head motion sensitivity of the vestibular nuclei neurons that mediate VSR (i.e., VO neurons) is substantially attenuated when the goal of the ongoing motor behavior is to generate voluntary motion of the head through space, rather than to stabilize head motion. In both of these situations, the attenuation is behaviorally advantageous since intact vestibular reflexes would likely be counterproductive, eliciting reflex responses that would oppose intended voluntary behaviors. The mechanisms underlying these two examples of behaviorally dependent processing of vestibular information at the first central stage of processing as well as the implications for behavior and higher-order vestibular processing are explicitly discussed in relation to the VOR and VSR below.

THE ROTATIONAL VESTIBULO-OCULAR REFLEX AND GAZE STABILIZATION

The VOR effectively stabilizes gaze during our everyday activities by moving the eye in the opposite direction to the ongoing head rotation. Numerous studies performed over many decades have well characterized the morpho-physiologic organization of the circuitry underlying the VOR (reviewed in Straka and Dieringer, 2004).

Neural circuitry mediating the vestibulo-ocular reflex

In 1933, Lorente de No first described the most direct pathway between the vestibular end organs and eye muscles, which is mediated by a three-neuron arc in which vestibular afferents project to neurons in the vestibular nuclei, that in turn project to extraocular motoneurons (Fig. 2.4). Subsequent studies have further demonstrated that the fundamental structure of VOR circuitry is well conserved following its establishment in early vertebrates (reviewed in Straka and Baker, 2013). Because of its relative simplicity in comparison to other sensorimotor circuits, the VOR has proven to be an excellent model system for bridging the gap between neuronal circuits and behavior.

Three properties of the VOR make it particularly well suited for stabilizing gaze. First, consistent with the synaptic and axonal delays of the three-neuron arc, the compensatory eye movements produced by the VOR lag head movements by only approximately 5 ms in the primate (Minor et al., 1999; Huterer and Cullen, 2002). Second, the VOR shows remarkably compensatory dynamics over physiologic relevant range of head movements (Armand and Minor, 2001; Huterer and Cullen, 2002) such that its gain (i.e., eye velocity/head velocity) is close to unity, and it shows minimal phase lag. Finally, not only does the VOR remain compensatory for high-frequency head rotations, but it does so for head velocities approaching 500°/s (Paige, 1983; Tomlinson, 1990).

The results of single-unit recordings in monkeys have provided insight into how the circuitry underlying the VOR effectively stabilizes gaze across the wide range of head frequencies and velocities experienced in everyday life (Cullen, 2012). Compensation for the small but finite 5-ms reflex pathway delay is provided by a frequency-dependent increase in neuronal response phase. Specifically, the responses of type I PVP neurons lead rotational head velocity and this lead increases from 10 to 60° for head motion at 0.5 Hz versus 15 Hz (Roy et al., 2003; Ramachandran and Lisberger, 2008). In contrast, compensation for high-velocity head rotations provides the match that exists between the nonlinear dynamics of direct VOR pathways and the complementary dynamics of the oculomotor plant itself. Notably, the responses of PVP neurons show a soft saturation for ipsilateral velocities >200°/s and are silenced for contralateral head velocities of 100–200°/s. These values are less than those that are generated during daily activities, raising the question of how the VOR remains compensatory for head rotations of up to 500°/s. Quantification of extraocular motoneurons during such high-velocity motion has revealed that these nonlinear properties of PVP neurons are effectively offset by the

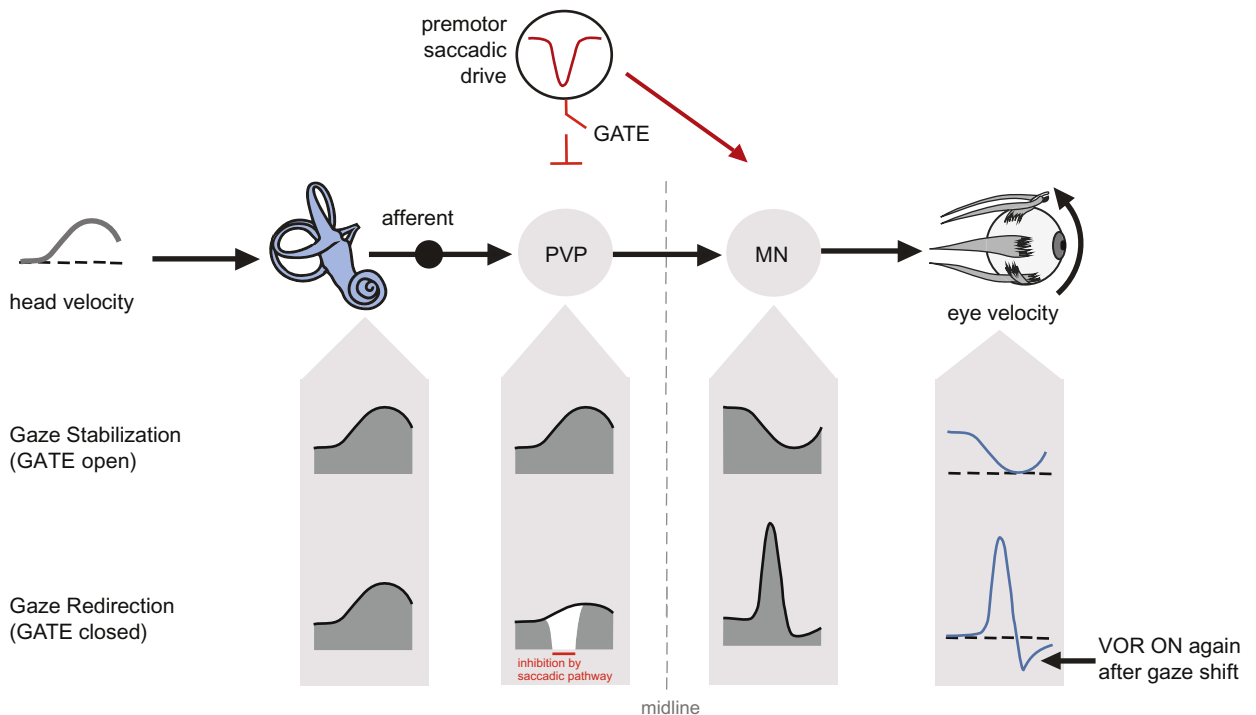


Fig. 2.4. Vestibulo-ocular reflex (VOR) pathway and the mechanism underlying VOR suppression during gaze redirection (i.e., gaze shifts). While the VOR is compensatory over a wide frequency range when the goal is to stabilize gaze, its efficacy is reduced during gaze shifts. Vestibular afferents encode head movements regardless of the behavioral goal. However, experiments in monkeys have shown that, at the next stage of processing, the responses of type I position-vestibular-pauses (PVPs) are suppressed during gaze shifts. The mechanism mediating this suppression is well understood. Specifically, the premotor saccadic pathway that drives gaze shifts via its direct projections to the extraocular motoneurons (MN; red arrow), also strongly inhibits the direct VOR pathway (i.e., closing the “gate” to send a suppression signal). This behaviorally dependent modulation of the VOR is depicted by the shaded panels below the circuit: (1) during gaze stabilization the “gate” remains open and the VOR pathway produces a compensatory eye movement, while (2) during gaze redirection, the “gate” is closed and the VOR pathway is attenuated by the inhibitory command from the saccadic pathway.

complementary dynamics of the oculomotor plant (Sylvestre and Cullen, 1999).

The efficacy of the vestibulo-ocular reflex is suppressed during voluntary gaze behaviors

The efficacy of the VOR is not constant, but instead depends on the behavioral context. Specifically, the VOR is modulated as a function of the current behavioral gaze goal. When the goal is to maintain stable gaze, the VOR is compensatory (Fig. 2.4). However, the efficacy of the VOR is altered during voluntary gaze behaviors. Behavioral studies in humans and primates have shown that the VOR is attenuated or even suppressed when humans and monkeys voluntarily redirect their gaze (eye/head and or body movements) towards a target of interest (Lauritis and Robinson, 1986; Pelisson and Prablanc, 1986; Tomlinson and Bahra, 1986; Guitton and Volle, 1987; Pelisson et al., 1988; Tomlinson, 1990; Tabak et al., 1996). During gaze shifts, VOR suppression is maximal early in the gaze shift and

progressively recovers to reach normal values by gaze-shift end (Cullen et al., 2004). In addition, the gain of the VOR varies as a function of vergence angle (Viirre et al., 1986; Crane and Demer, 1998).

The results of single-unit recordings in monkeys have provided insight into the mechanisms that modulate the efficacy of the direct VOR pathways during voluntary gaze behaviors. Specifically, the head movement-related modulation of PVP neurons is markedly reduced while monkeys redirect their visual axis of gaze using combined eye-head-orienting gaze shifts or pursuit (Roy and Cullen, 1998, 2002; McCrea and Gdowski, 2003). The mechanism mediating this attenuated response is an inhibitory projection to the vestibular nuclei from brainstem premotor saccadic and pursuit pathways (reviewed in Cullen, 2012). Specifically, when gaze is purposefully redirected using either the saccadic or smooth-pursuit pathways, a copy of the premotor motor command that drives the redirection of gaze is sent to the vestibular nuclei to suppress the head movement-related modulation of PVP neurons (Fig. 2.4, gate closed versus

open). Indeed, inhibiting the direct VOR pathways with a copy of the motor command to voluntarily redirect gaze is advantageous in this situation, since an intact VOR movement would function to drive the eye in the opposite direction to the intended change in gaze.

As noted above, the efficacy of the direct VOR pathway is also modulated as a function of viewing distance, as gaze is used to orient the visual axis on a near or far target. This is because the eyes translate as well as rotate relative to space since they cannot both be perfectly aligned with the axis of rotation (Vierre et al., 1986). Consequently, for the same amplitude of head rotation, a larger VOR gain is necessary to stabilize a near than a far earth-fixed target. Differences in the responses of the PVP neurons that mediate the direct VOR pathways are consistent with these distance-related changes in VOR gain (Chen-Huang and McCrea, 1999).

Vestibular compensation and motor learning

The VOR is capable of remarkable compensation following peripheral vestibular loss (human: Gonshor and Melvill Jones, 1976; Allum et al., 1988; Curthoys and Halmagyi, 1995; macaque monkey: Sadeghi et al., 2006). This compensation is critical to maintain accurate perception and motor performance with the loss of vestibular hair cells that occurs as a result of normal aging, as well as to recover from disorders that affect hair cells or afferents (e.g., vestibular nerve neuromas, vestibular neuritis, or trauma). In addition, the vestibular system is capable of impressive adaptation to environmental requirements. This adaptability of the VOR circuitry is vital in the first years of life to compensate for significant changes in head circumference (~30% in the first year), as well as in later life to compensate for common conditions such as the need to wear corrective lenses for visual conditions such as myopia (i.e., nearsightedness). Vestibular scientists have long appreciated the impressive adaptive capabilities in the VOR. For example, in 1976 Gonshor and Melvill Jones asked subjects to view the world through reversing prisms continually for 3–4 weeks. Theoretically the direction of the VOR would need to be reversed to stabilize the world on the retina during head movements with this new “environmental requirement.” Indeed, subjects showed adaptive changes in their VOR changes that were consistent with the imposed (and exceptionally challenging) requirements of retinal image stabilization during head movement, indicating extensive and retained learning within the reflex pathway.

VESTIBULAR COMPENSATION

Within a month of peripheral vestibular loss, VOR compensation is nearly complete for rotations toward the contralesional side, as well as for less challenging

(i.e., lower-frequency and velocity) rotations toward the ipsilesional side (Smith and Curthoys, 1989; Cullen et al., 2009). Compensation processes, however, are not able to fully restore the VOR for more challenging ipsilesional rotations (Halmagyi et al., 1990; Gilchrist et al., 1998; Sadeghi et al., 2006). Our understanding of the basic mechanisms mediating vestibular compensation following peripheral loss has greatly advanced over the past several decades. Single-unit recording experiments in monkeys revealed a small but significant increase in the irregularity of vestibular afferents in the remaining intact contralesional nerve (Sadeghi et al., 2006). This effect might be mediated by compensatory mechanisms involving the vestibular efferent system, which originates from a group of cells near the abducens nucleus in the brainstem and projects back to the vestibular periphery (reviewed in Goldberg, 2000). Furthermore, long-term changes in the strength of the commissural connections between the vestibular nuclei play an important role in compensation (Dieringer and Precht, 1979a, b). Specifically, GABAergic inhibition is reduced on the impaired side, producing a change in the strength of cerebellar input to the vestibular nuclei (reviewed in Straka et al., 2005). *In vitro* experiments have further shown that compensation is accompanied by changes in intrinsic properties of cells on both the contra- and ipsilesional sides (Beranek et al., 2003, 2004).

In vivo studies in cats and monkeys have provided insight into the time course of the functional changes occurring at the level of specific neurons within the VOR pathways to drive compensation. Immediately following a unilateral peripheral lesion, there is a decrease in the resting discharge of vestibular cells on the ipsilesional side and an increase on the contralesional side (Ris et al., 1995; Ris and Godaux, 1998). This asymmetry underlies the static symptoms that are observed clinically, such as spontaneous nystagmus and head tilt toward the side of the lesion (Curthoys and Halmagyi, 1995; Sadeghi et al., 2006). Recent experiments in behaving monkeys have further shown that the sensitivities of contralateral type I PVP neurons substantially decrease immediately after unilateral vestibular loss, and then recover within a month, reaching values close to those measured before the lesion (Sadeghi et al., 2010). Thus, this improvement in the VOR pathway neurons provides a neural correlate for the dynamic improvement in the VOR performance that is observed over the same timeframe.

Research on basic physiologic mechanisms has further revealed that homeostatic plasticity plays a fundamental role in vestibular compensation. Recent single-unit studies in rhesus monkeys have shown that compensation is mediated by rapid dynamic reweighting of inputs from different modalities (i.e., extr vestibular proprioception and motor efference copy signals versus

vestibular signals) at the level of vestibular nuclei neurons (Sadeghi et al., 2010, 2011, 2012; Jamali et al., 2014). In particular, within a day of vestibular loss, type I PVP neurons become responsive to passive stimulation of proprioceptors (note, they are insensitive to such stimulation under normal conditions). In turn, this rapid unmasking of sensitivity to proprioceptive input is linked to faster and more substantial recovery of the neuronal resting rates (Sadeghi et al., 2010). Moreover, in the weeks that follow peripheral vestibular loss, type I PVP neurons also become responsive to motor efference copy input. Thus, multimodal integration is dynamically regulated in the vestibular system in a manner that suggests a causal role for homeostatic plasticity in VOR compensation. It is noteworthy that this strategy is common across different animal species (Dichgans et al., 1973; Newlands and Perachio, 1991; Ris and Godaux, 1998; Vibert et al., 1999; Newlands et al., 2001; Straka et al., 2005), as well as humans (Della Santina et al., 2001, 2002), and likely provides the neural substrate for rehabilitation approaches currently used by clinicians to treat patients. For instance, Cawthorne–Cooksey exercises along with other popular training approaches promote compensation by combining stimulation of vestibular and extr vestibular (i.e., proprioceptive and motor efference copy) inputs in patients (Ricci et al., 2010).

MOTOR LEARNING

Plasticity within vestibular pathways is also essential for fine-tuning the coordination and accuracy of the VOR in response to environmental requirements. Because of its relative simplicity and precise behavioral readout (i.e., eye movements), the VOR circuitry has become a popular model system for investigating how changes in single-neuron responses lead to adaptive modification of circuit function and motor behavior. In particular, to understand the physiologic mechanism of sensorimotor learning, it is necessary to link changes in the patterns of neural activity with specific changes in performance. The cerebellar-based mechanisms mediating VOR motor learning have been extensively characterized (Boyden et al., 2004; Straka and Dieringer, 2004; Cullen, 2008; Medina, 2011). Experiments in alert-behaving animals have shown that initially plasticity within the floccular complex of the cerebellum drives VOR adaptation (Kassardjian et al., 2005; Broussard et al., 2011). These changes then initiate longer-term synaptic changes in target neurons within the vestibular nuclei, specifically in the group of neurons called floccular target cells or EH neurons (Broussard and Lisberger, 1992). *In vivo* and *in vitro* studies further suggest that plasticity occurs within noncerebellar VOR pathways (Beranek et al., 2008;

McElvain et al., 2010; Scarduzio et al., 2012) alongside synaptic changes within the cerebellum to ensure a relatively robust behavioral output. Thus, to ensure accurate motor performance, multiple sites of plasticity shape motor performance even in simple pathways such as the VOR.

VESTIBULOSPINAL AND VESTIBULOCOLIC REFLEXES

In addition to its crucial role in stabilizing the eye relative to space via the VOR, the vestibular system also coordinates postural reflexes. VSRs such as the vestibulocolic reflex (VCR) are critical for maintaining head and body posture during our daily activities. The VCR functions to stabilize the head relative to inertial space by generating a command to move the head in the opposite direction to that of the current head-in-space velocity (Ezure and Sasaki, 1978; Peterson et al., 1981; Baker et al., 1985; Goldberg and Peterson, 1986; Wilson et al., 1990). VO neurons in the VN project to the cervical spinal cord and are thought to mediate the VCR pathway (Fig. 2.5) (Wilson et al., 1990; Boyle, 1993; Boyle et al., 1996; Gdowski and McCrea, 1999). Additionally, projections from vestibulospinal axons to both the cervical and/or lumbar levels of the spinal cord (Abzug et al., 1974; Rapoport et al., 1977; Shinoda et al., 1988) coordinate different parts of the musculature, for example, the neck and axial muscles during head movement to ensure stable posture.

Neural circuitry mediating the vestibulospinal reflex

Similar to the VOR, the most direct pathway connecting the vestibular nerve and spinal cord motoneurons is a three-neuron arc. The summed delays of this direct VSR pathway include the time required for: (1) neural transduction; (2) afferent spike train initiation; (3) synaptic transmission; and (4) conduction times – accounting for a few extra milliseconds required for the longer conduction pathways to the motoneurons of the spinal cord. Indeed, consistent with this direct pathway, vestibular-evoked myogenic potentials first appear ~10 ms following brief clicks played through headphones (i.e., Colebatch et al., 1994). Moreover, these neck muscle-level responses are abolished following vestibular neurectomy, confirming they are driven by vestibular reflexes (Colebatch et al., 1994). However, in response to vestibular stimulation, the latency of the actual compensatory head movement generated by the VSR is >30 ms (VCR: Wilson and Maeda, 1974; Mitchell et al., 2013). There are three key reasons why this latency of movements produced by the VSR is markedly longer than that of the eye movements generated by VOR (~5 ms).

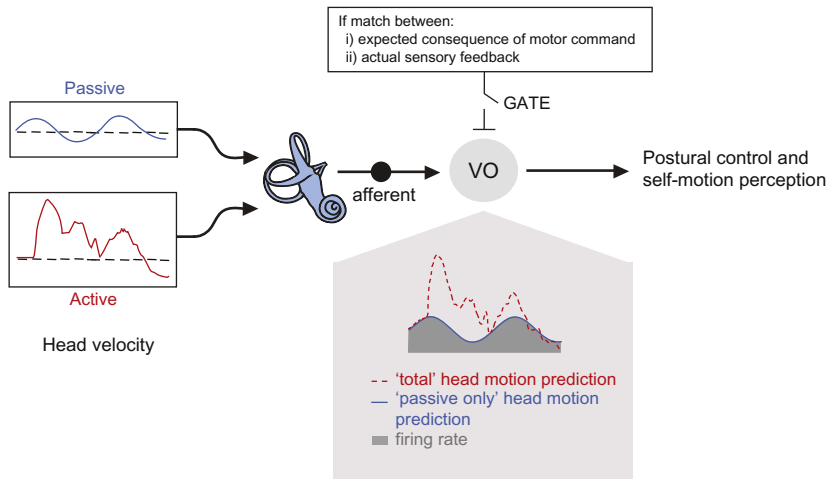


Fig. 2.5. Vestibular-only (VO) neurons and the mechanism underlying their suppression during active head motion. Vestibular afferents encode head movements regardless of whether vestibular stimulation is the result of head motion that is actively generated (vestibular reafference) or passively applied (vestibular exafference). However, during active head movement, VO neurons receive a strong inhibitory input (“gate”) that effectively suppresses their responses. In particular, vestibular reafference is canceled when there is a match between the expected sensory consequence of neck motor command and the actual neck proprioceptive feedback.

First, the latency from spinal motoneuron stimulation to head motion onset is ~ 20 ms (Elsley et al., 2007) – a value significantly longer than the ~ 3 ms latency between oculomotor neuron stimulation, muscle contraction, and movement (Fuchs and Luschei, 1971). Second, the relatively longer latencies of evoked head motion are consistent with the relatively sluggish dynamics of the neck versus eye plant (Zangemeister et al., 1981; Peng et al., 1996, 1999). Finally, the dominant pathways mediating the VSR are more complex and involve additional structures, including the interstitial nucleus of Cajal, dorsal lateral vestibular nuclei, and medial reticular formation (reviewed in Goldberg and Cullen, 2011).

The efficacy of the vestibulospinal reflex is markedly reduced during active movement

As described above for the VOR, the efficacy of the VSR is not constant but instead depends on the behavioral context. Specifically, VSR pathways are suppressed when the current behavioral goal is to voluntarily move the head relative to the world. The results of single-unit recordings in monkeys have provided insight into the mechanism that is responsible for modulating the efficacy of the direct VSR pathways during voluntary motion.

Vestibular afferents similarly encode self-generated and externally applied head motion (Cullen and Minor, 2002; Sadeghi et al., 2007; Jamali et al., 2009). However, when head movements are self-produced, the head velocity-related responses of VO neurons in the vestibular nuclei are dramatically reduced (McCrea et al., 1999;

Roy and Cullen, 2001, 2004; Brooks and Cullen, 2013; Carriot et al., 2014, 2015). Additionally, the head velocity-related responses of these same neurons are similarly attenuated when the head moves in space as a result of voluntary head-on-body motion or body motion (Brooks and Cullen, 2013). The suppression of vestibular input that is the result of head motion produced either by activation of the neck musculature (head-on-body motion) or axial muscles that move the head and body (e.g., orienting body movements; McCluskey and Cullen, 2007; Anastasopoulos et al., 2009) is comparable. Moreover, the level of suppression is striking: in rhesus monkeys vestibular responses are attenuated by $\sim 70\%$ during active rotations and translations (Roy and Cullen, 2001, 2004; Brooks and Cullen, 2013; Carriot et al., 2014, 2015).

Importantly, VO neurons can also selectively respond to passive head motion during combined active and passive motion. For example, when monkeys produce active head-on-body movements while undergoing passive whole-body rotation, VO neurons preferentially respond to the passive component of the vestibular stimulation (Roy and Cullen, 2001; Brooks and Cullen, 2013; Carriot et al., 2014). A series of studies in which the correspondence between intended and actual head movement was experimentally controlled have provided insight into the mechanism that accounts for this striking suppression. Specifically, evidence to date suggests that vestibular input to these neurons is suppressed when there is a match between the predicted and actual proprioceptive sensory feedback during self-motion (i.e., the gate would close in Fig. 2.5: Roy and Cullen, 2004; Brooks and Cullen, 2013, 2014; Carriot et al., 2013).

The differential processing of passive versus active head motion: functional implications

The behaviorally dependent gating of vestibular responses at the level of the vestibular nuclei has significant implications for understanding how the brain ensures accurate posture and motor control during self-motion. In addition, the differentiation of sensory stimulation that arises from passive versus active movement is required for perceptual stability.

First, the reduced sensitivity of these neurons during active head movements is consistent with their functional role in the vestibulospinal pathways that ensure the maintenance of stable posture and balance (reviewed in [Cullen, 2011, 2012](#)). In particular, their selective and robust response to unexpected passive vestibular stimulation is behaviorally advantageous, producing the required compensatory reflex responses (e.g., recovery from tripping over an obstacle). Likewise, their attenuated responses to expected active vestibular stimulation are behaviorally advantageous. This is because the same VSRs that are needed to compensate for unexpected motion would actually be counterproductive during self-generated movements (they would oppose the intended motion). Thus, it is vital to reduce the efficacy of the VSR during active movements. Importantly, in addition to their descending projection to the spinal cord, VO neurons have reciprocal connections with regions of the cerebellum that are vital for the control of posture and spatial orientation, including the rostral fastigial nucleus ([Shimazu and Smith, 1971](#); [Batton et al., 1977](#); [Carleton and Carpenter, 1984](#); [Homma et al., 1995](#)) and the nodulus/uvula ([Walberg and Dietrichs, 1988](#); [Xiong and Matsushita, 2000](#)). Accordingly, the ability of these neurons to preferentially encode unexpected motion also likely contributes to the fine-tuning of motor commands ([Brooks et al., 2015](#)).

Second, prior studies have shown that a match between sensory feedback and the causal motor command is required for accurate sensation. Indeed, the differential processing of vestibular sensory input observed in early vestibular processing parallels findings for other voluntary behaviors, for instance, self-produced tactile stimulation ([Blakemore et al., 1999, 2000](#)) and perceived force during tapping ([Bays et al., 2005](#)) and lifting tasks ([Diedrichsen et al., 2003, 2005](#)). This suggests a common strategy across sensory systems regarding the suppression of self-generated sensory inputs. As discussed below, VO neurons provide vestibular information to cortical areas involved in the computation of self-motion perception and orientation ([Deecke et al., 1977](#); [Meng et al., 2007](#); [Marlinski and McCrea, 2008](#); [Meng and Angelaki, 2010](#)) through their ascending projections to the thalamus ([Wild, 1988](#); [Shiroyama et al., 1999](#);

[Zwergal et al., 2009](#)). Thus, the differential coding of passively versus actively generated motion by VO neurons also contributes to perceptual stability during self-motion (i.e., was my motion intended or unexpected?).

HIGHER-ORDER VESTIBULAR PROCESSING

Historically, basic research on the physiology of central vestibular pathways has predominantly focused on the circuitry that mediates reflex pathways such as the VOR and VSR. Studies of patients with vestibular loss have underscored how vital these reflexes are in our everyday lives. In addition, the vestibular system plays fundamental roles in providing our perception of self-movement, spatial orientation, and body representation (reviewed in [Mast et al., 2014](#)). Recent neurophysiologic experiments in nonhuman primates have furthered our understanding of the computations performed by the vestibular cerebellum and cortex. These findings are complemented by neuroimaging studies in humans using caloric and galvanic vestibular stimulation that have advanced our knowledge of how these higher-order structures encode and process vestibular stimuli (reviewed in [Dieterich and Brandt, 2008, 2010](#)).

Vestibular cerebellum

There are five main regions of the cerebellum ([Fig. 2.6](#)) that receive either primary (i.e., from afferents) or secondary (i.e., from vestibular nuclei) vestibular input including the: (1) nodulus and ventral uvula (lobules X and IX); (2) flocculus and ventral paraflocculus; (3) oculomotor vermis of posterior lobe (lobules VI–VII); (4) lobules I–V of the anterior lobe; and (5) deep cerebellar nuclei. As described below, each of these regions makes an important contribution to the processing of vestibular sensory information.

The vestibular nuclei are reciprocally interconnected with the nodulus/uvula of the cerebellum ([Wearne et al., 1998](#)). Lesions of both cerebellar structures alter the temporal and three-dimensional spatial processing of vestibular information (reviewed in [Goldberg et al., 2012](#)), suggesting it makes significant contributions to the computation of inertial motion ([Angelaki and Hess, 1995](#); [Wearne et al., 1998](#)). Recent experiments have provided specific insight into the computations performed within these cerebellar lobules to distinguish head tilt from translation. Einstein's equivalence principle indicates that the otolith organs and, in turn, otolith afferents, will not distinguish linear accelerations that are due to head tilts (relative to gravity) from those that are the result of translational self-motion. However, the activation of the semicircular canals differs in these two conditions, because semicircular canals are stimulated by the

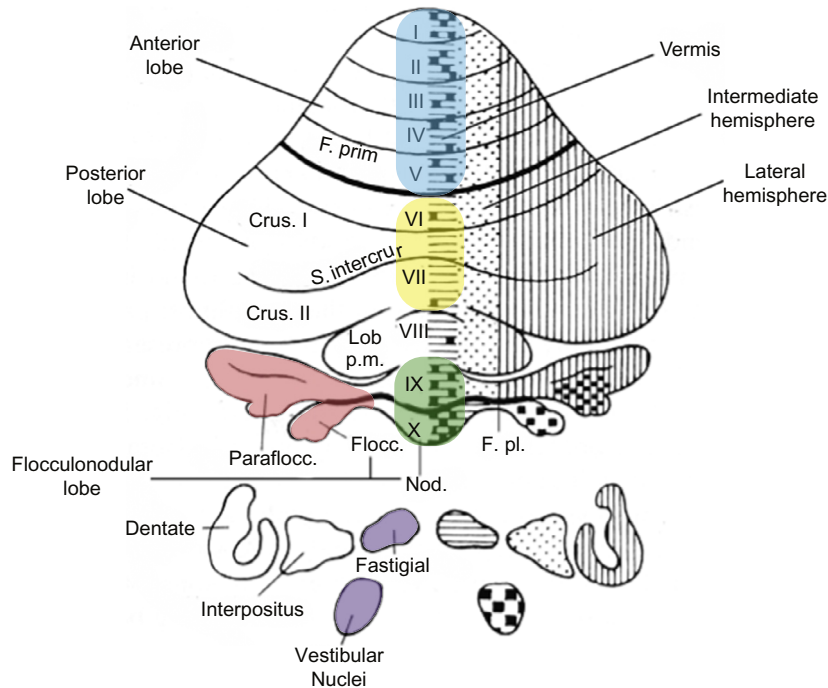


Fig. 2.6. Schematic of the cerebellar cortex with the divisions denoted between the anterior, posterior, and flocculonodular lobes along the rostral–caudal axis. Perpendicular to this, along the medial–lateral axis, the cerebellum can also be divided into three longitudinal zones, including the vermis (I–X), intermediate, and lateral hemispheres, which project to different deep cerebellar nuclei, namely the fastigial, interpositus, and dentate respectively, as well as vestibular nuclei. The main cerebellar regions that receive vestibular input include the nodulus and ventral uvula (green), flocculus and ventral paraflocculus (red), oculomotor vermis of posterior lobe (yellow), lobules I–V of the anterior lobe (blue), and fastigial deep cerebellar nucleus and vestibular nuclei (purple). Flocc., flocculus; Lob. p.m., paramedian lobule; Nod., nodulus; Paraflocc., paraflocculus; S. intercrur, intercrural sulcus. (Adapted from Brodal, 1979.)

rotations accompanying head tilt but not by pure translations. Thus, by integrating these two signals, the brain can theoretically distinguish between tilt and translation (Mayne, 1974; Merfeld, 1995; Angelaki et al., 1999; Merfeld et al., 1999, 2001, 2005; Bos and Bles, 2002; Green et al., 2005; Green and Angelaki, 2007; Laurens and Droulez, 2007; Laurens and Angelaki, 2011; Laurens et al., 2011; Zupan et al., 2002). Recent single-unit recording studies in the nodulus and uvula of monkeys suggest the brain explicitly performs such a computation such that some Purkinje cells combine otolith and semicircular canal inputs to encode translation (Yakusheva et al., 2007), while other cells encode tilt (Laurens et al., 2013).

The flocculus and adjoining paraflocculus are involved in the generation and plasticity of compensatory eye movements, including visual ocular following reflexes (i.e., smooth-pursuit and OKR) and the VOR (Lisberger and Fuchs, 1978; Noda and Suzuki, 1979; Miles and Braitman, 1980; Miles et al., 1980; Buttner and Waespe, 1984; Lisberger et al., 1994a, b). As discussed above, this region of the cerebellum plays a vital role in VOR compensation and motor learning (Boyden

et al., 2004; Straka and Dieringer, 2004; Cullen, 2008; Medina, 2011), such that during motor compensation and learning, synaptic changes within the floccular complex drive changes in the VOR pathways, which are required to ensure compensatory performance. Lobules VI and VII of the vermis – an area commonly referred to as the oculomotor vermis – are also involved in visual-vestibular processing (Suzuki and Keller, 1982, 1988; Sato and Noda, 1992). In addition to vestibular input, the oculomotor vermis receives eye movement signals from the nucleus prepositus (Belknap and McCrea, 1988) as well as pursuit-related inputs from the dorsolateral pontine nuclei (Brodal, 1979; Yamada and Noda, 1987). This latter region receives input from cortical regions, including the middle temporal and medial superior temporal pursuit areas (Glickstein et al., 1980).

Finally, the vestibular nuclei are reciprocally interconnected with the deep cerebellar nuclei and anterior vermis of the cerebellum (Batton et al., 1977). The anterior region of the cerebellar vermis (lobules I–V) encodes both vestibular and neck proprioceptive-related signals (Manzoni et al., 1998a, b, 1999, 2004) and is involved in the control of VSR. The integration of

vestibular and proprioceptive information ensures that the motor responses produced by these reflexes are appropriate to maintain body stability. The anterior vermis sends strong descending projections to the rostral fastigial nucleus (the most medial of the deep cerebellar nuclei), which also receives proprioceptive input via the central cervical nucleus and the external cuneate nucleus (Voogd et al., 1996). The rostral fastigial nucleus is a critical component of the descending pathway controlling postural reflexes and orienting behaviors; it projects to brainstem structures that control these behaviors, including the vestibular nuclei and medial reticular formation. Many neurons in the rostral fastigial nucleus integrate vestibular and proprioceptive inputs, and in turn encode vestibular signals in a body-centered reference frame (Kleine et al., 2004; Shaikh et al., 2004). In addition, rostral fastigial nucleus neurons encode externally applied head and body-in-space motion in two distinct streams (Brooks and Cullen, 2009). Importantly, these same rostral fastigial nucleus neurons are unresponsive to self-generated head and body motion, suggesting that the cerebellum computes an internal model of the expected sensory consequences of active head motion to selectively cancel responses to active motion (Brooks and Cullen, 2013). This mechanism is likely responsible for the attenuation during active motion observed in early vestibular processing discussed above, and is essential for ensuring accurate spatial orientation and postural control during everyday activities.

Vestibular cortex

The vestibular nuclei and vestibular cerebellum send projections to the regions of the thalamus that are sensitive to vestibular stimulation (reviewed in Lopez and Blanke, 2011). In turn, these regions of the thalamus send ascending projections to areas of cortex. However, unlike visual, auditory, or somatosensory systems, there is no single primary cortical area processing information in the vestibular system. Notably, most neurons in regions of the thalamus and cortex that receive direct and indirect inputs from the vestibular nuclei receive convergent vestibular, visual, and somatosensory inputs (Akbarian et al., 1988, 1992), emphasizing the inherently multimodal nature of vestibular processing.

Neurophysiologic studies have established that vestibular-related activity is found in multiple regions of the cerebral cortex (Fig. 2.7), including: area 2v of the intraparietal sulcus (Buttner and Buettner, 1978), area 3a in the sulcus centralis (Odkvist et al., 1974), ventral intraparietal area (Bremmer et al., 2002), medial superior temporal area (Duffy, 1998) and parietoinsular vestibular cortex (PIVC) (Grusser et al., 1990). Single-unit recording experiments in the ventral intraparietal area in area 7

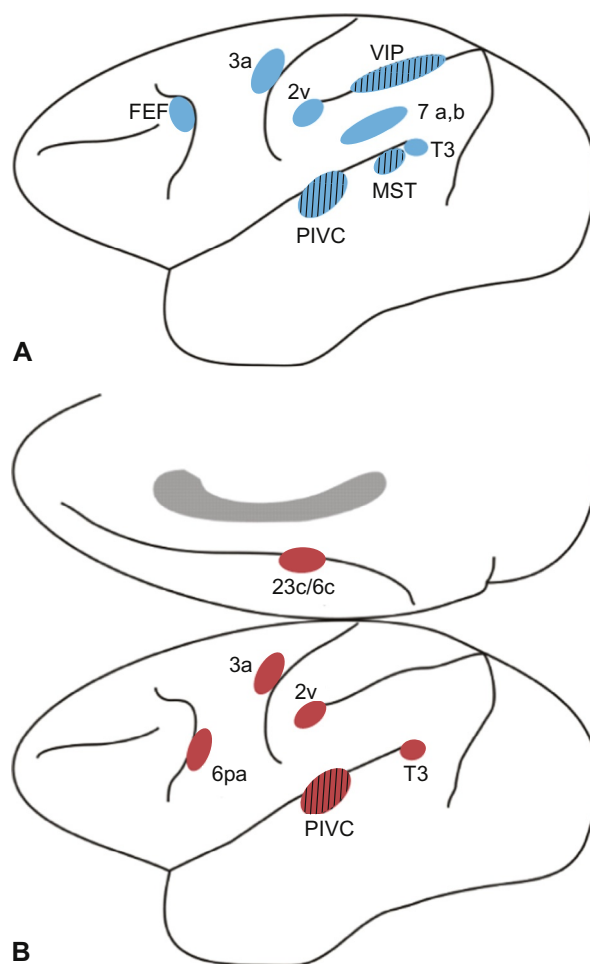


Fig. 2.7. Schematic representation of vestibular cortical areas in monkey. **(A)** Areas of cortex that receive inputs from vestibular nuclei. **(B)** Cortical areas that project back to the vestibular nuclei. FEF, frontal eye field; MST, medial superior temporal; VIP, ventral intraparietal; PIVC, parietoinsular vestibular cortex. Numbers refer to specific Brodmann areas of the cerebral cortex. Striped areas are deep cortical areas, and the gray shaded region in **(B)** denotes the corpus callosum.

found different activity in response to active and passive head movements, including changes in the strength, timing, and direction selectivity of their responses under the two conditions (Bremmer et al., 2002; Klam and Graf, 2003, 2006). This differential encoding of vestibular information is important for shaping appropriate motor responses to guide voluntary movements.

Of all these cortical areas, PIVC is commonly thought to be the most critical for shaping our perception of self-movement, spatial orientation, and body representation. Stimulation of this area has long been known to produce vestibular sensation in humans (Penfield, 1957), and PIVC lesions impair the perception of subjective vertical (Brandt et al., 1994). Additionally, PIVC receives convergent information from many of the other cortical areas

in which vestibular-related activity has been reported (reviewed in [Guldin and Grusser, 1998](#)) and cerebral blood flow of PIVC increases during vestibular stimulation ([Friberg et al., 1985](#)). Recent electrophysiologic studies have also focused on vestibular processing in the dorsal medial superior temporal cortex (MSTd) (reviewed in [Angelaki et al., 2011](#)). Specifically, this cortical area, long known to process optic flow information for visual following and smooth-pursuit eye movements, is also thought to play a role in representing heading direction ([Duffy, 1998](#); [Page and Duffy, 2003](#)). Experiments demonstrating a functional link between area MSTd and heading perception based on vestibular signals further suggest that this region plays a role in self-motion perception ([Fetsch et al., 2007](#); [Gu et al., 2007](#)). Finally, the transmission of self-motion information from these cortical areas to areas such as entorhinal and perirhinal cortices, and hippocampus likely play a critical role in spatial cognition and navigation (reviewed in [Hitier et al., 2014](#)).

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