


Vestibular processing during natural self-motion: implications for perception and action

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Abstract | How the brain computes accurate estimates of our self-motion relative to the world and our orientation relative to gravity in order to ensure accurate perception and motor control is a fundamental neuroscientific question. Recent experiments have revealed that the vestibular system encodes this information during everyday activities using pathway-specific neural representations. Furthermore, new findings have established that vestibular signals are selectively combined with extr vestibular information at the earliest stages of central vestibular processing in a manner that depends on the current behavioural goal. These findings have important implications for our understanding of the brain mechanisms that ensure accurate perception and behaviour during everyday activities and for our understanding of disorders of vestibular processing.

Linear rate code

A neural code in which the frequency of action potentials fired by a neuron (that is, the firing rate) is linearly related to the intensity of the stimulus.

Vestibulo-ocular reflex

(VOR). A reflex that moves the eye in the opposite direction of the ongoing head motion to stabilize the visual axis of gaze relative to the environment.

Vestibulo-spinal reflex

A reflex that activates the neck and/or skeletal muscles to stabilize the body in order to maintain posture and balance.

The vestibular system generates reflexes that are vital for providing stable gaze and maintaining posture during our daily activities. This essential sensory system also makes important contributions to our perception of self-motion and spatial orientation. Because vestibular information is integrated with other sensory signals (including visual and proprioceptive signals) and motor signals, we are usually unaware of a distinct sensation arising from the vestibular system in everyday life. However, studies of patients with vestibular sensory loss have highlighted its essential role. During normal daily activities, these patients experience debilitating gaze instability and postural imbalance (reviewed in REF.¹). Although the brain can, over time, learn to better utilize the self-motion cues provided by other sensory systems and motor-related signals^{2,3}, this sensory substitution strategy can never fully compensate. As a result, patients report gaze instability as well as other motion-induced symptoms that make activities requiring dynamic head movements challenging.

The prevailing view has long been that the mammalian vestibular system uses a linear rate code to represent sensory information (reviewed in REF.⁴). This view has provided a foundation for quantitative studies and modelling of the neural circuits that control and calibrate 'simple' sensorimotor transformations including the vestibulo-ocular reflex (VOR) and the vestibulo-spinal reflex. However, recent findings have revealed that in everyday life the processing that takes place at early stages of mammalian vestibular pathways is actually strongly nonlinear⁵⁻⁹. Notably, these findings have shown that well-established linear models of early

vestibular processing are only valid over an extremely restricted range of movements and do not explain how vestibular pathways represent the stimuli encountered during everyday activities. Moreover, during voluntary movements, the information transmitted by the early stages of vestibular pathways is strongly regulated by the current behavioural goal¹⁰⁻¹⁷.

In this Review, I consider recent work that has furthered our understanding of the mechanisms by which natural self-motion is encoded and then combined with multimodal sensory and motor information, focusing on the role of this integration in the shaping of sensory processing for both perception and action. In addition, I review evidence linking vestibular loss to spatial memory and spatial navigational impairments in normal ageing and disease. Together, the findings described support a new view of the vestibular system in which the inherently nonlinear and context-dependent processing of vestibular afferent input underlies accurate behaviour and perceptual stability.

Early vestibular encoding

Vestibular encoding pathways. In mammals, the vestibular system is composed of five sensory organs within the inner ear: the three semicircular canals and the two otoliths (the utricle and saccule). Receptor cells (hair cells; FIG. 1a) within the semicircular canals sense head rotation in three orthogonal planes, whereas those in the otolith organs sense linear head acceleration (gravity and translational acceleration) in three dimensions. In turn, the afferent fibres of the vestibular nerve (a branch of the VIII nerve) transmit this information to central vestibular

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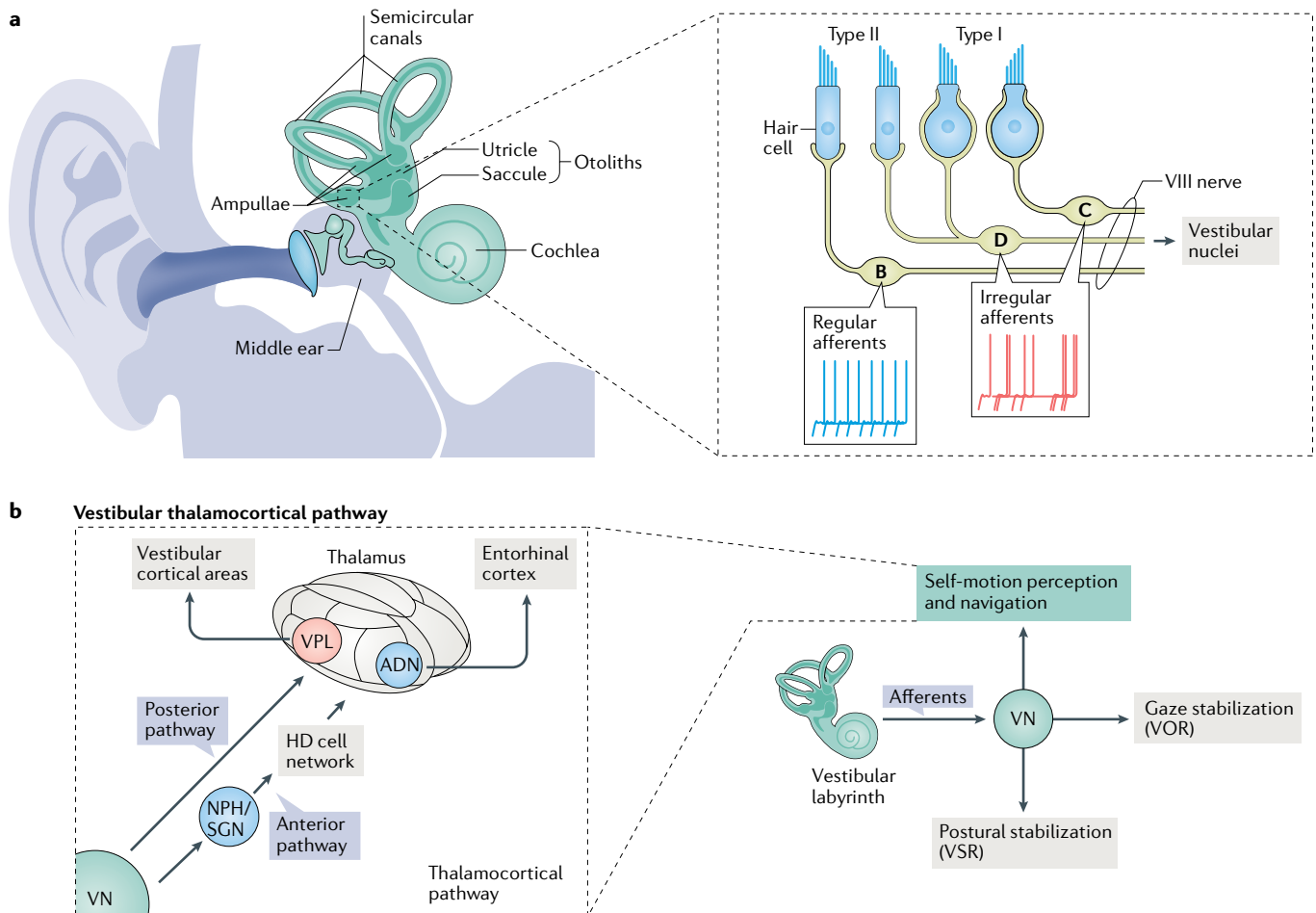


Fig. 1 | Overview of the vestibular labyrinth and central pathways. a | The vestibular labyrinth comprises five end organs: the three semicircular canals and the two otoliths (utricle and the saccule). In mammals, there are two types of hair cell within each of the vestibular sensory organs: cylindrical type II hair cells and the phylogenetically older flask-shaped type I hair cells. Peripheral afferents in cranial nerve VIII innervate hair cells and carry head movement signals to the vestibular nuclei and to some regions of the vestibular cerebellum. Each semicircular canal afferent innervates one of the three canals and encodes information about angular head motion. Otolith afferents innervate either the utricle or saccule and encode information about translational acceleration. Notably, otolith afferents respond to the inertial forces produced by translational motion through the environment or by changes in head orientation relative to gravity. Both canal and otolith afferent fibres are classified on the basis of the regularity of their resting discharge (reviewed in REFS^{4,27}). In general, irregular afferents have larger axons and preferentially transmit information from either the type I hair cells located at the centre of the neuroepithelium (known as C-irregulars) or from both type I and type II hair cells (known as dimorphic or D-irregulars), whereas regular afferents preferentially provide bouton (B) endings to type II hair cells. **b** | The vestibular system makes essential contributions to our perception of self-motion and ability to navigate as well as to vital reflex pathways (the vestibulo-ocular reflex (VOR) and the vestibulo-spinal reflex (VSR)). Vestibular information is sent to the cortex via two ascending vestibular thalamocortical pathways: the anterior vestibulothalamic pathway, comprised of projections from the vestibular nuclei (VN) to the nucleus prepositus and supragenual nucleus (NPH/SGN) and then on to the anterior dorsal thalamus (ADN) via the head direction (HD) network and the posterior vestibulothalamic pathway, comprised of projections from the VN through the ventral posterior lateral nucleus (VPL).

pathways. Thus, together, the vestibular sensory organs detect head movement in six dimensions (three axes of translation and three axes of rotation) to provide the brain with a real-time estimate of self-motion during everyday life required for a wide range of functions, from reflexes to the highest levels of voluntary behaviour^{4,18} (FIG. 1b).

The vestibular afferents that innervate the semicircular canals and the otoliths in mammals are classified as either regular or irregular on the basis of their resting discharge variability (FIG. 1a; reviewed in REF.¹⁹). Common wisdom has long held that both classes of

afferents and their target neurons in the vestibular nuclei encode head motion in a linear manner; that is, the relationship between their firing activity and the stimulus (head motion) obeys the superposition principle (reviewed in REFS^{4,19}). Indeed, the application of linear systems analysis to the vestibular system has provided important insights about how head motion is encoded in mammals. Specifically, vestibular afferents display high-pass tuning; the magnitude of their response modulation progressively increases for higher-frequency stimuli. Additionally, afferent responses increasingly lead

Superposition principle
The principle that, for all linear systems, the net response to two or more stimuli is the sum of the responses to each stimulus individually (also known as the superposition property).

High-pass tuning

A neuronal property in which the neuronal response becomes increasingly more sensitive as the frequency of stimulation becomes higher.

Phase leads

Advances in the phase (position within a cycle) of responses relative to an input sinusoidal waveform.

the stimulation waveform for higher-frequency stimuli (BOX 1). Moreover, irregular afferents demonstrate more sensitive responses and greater phase leads than regular afferents. Central neurons in the vestibular nuclei also typically show high-pass tuning^{5,20}. Importantly, however, these conclusions^{19,21,22} were based on linear modelling assumptions that are subject to important limitations (see below). The characteristics described above were demonstrated when neurons were tested with stimuli of relatively low intensity (rotational head

velocities of <50 deg s⁻¹ or linear head accelerations of 0.2 G) and low frequency (<1 Hz), which effectively constrain neurons to operate within their linear range.

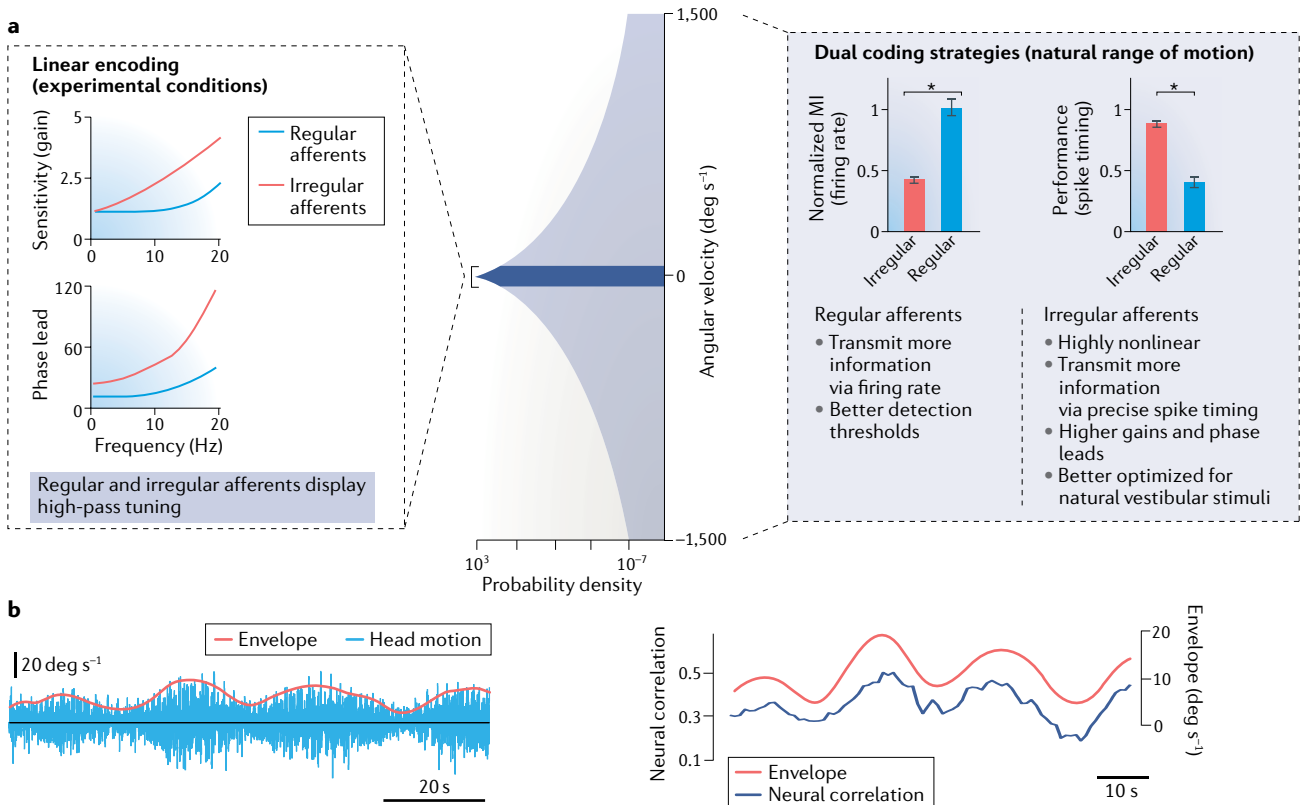
Statistics of natural self-motion. A number of recent studies have explicitly quantified the characteristics of the vestibular stimuli experienced during natural behaviours such as walking, running and foraging in humans²³, rhesus monkeys^{6,24} and rodents^{24,25} (BOX 1). Notably, it is now obvious that natural stimuli routinely reach

Box 1 | Vestibular coding strategies

Recent studies have revealed that the coding of head motion by vestibular afferents involves different strategies, depending on the dynamic range of stimulation. When head motion stimulation is at low frequencies and is limited to amplitudes within the linear amplitude range, such as those typically applied in laboratory experiments, canal and otolith afferents respond roughly in phase with fluctuations in rotational velocity and translational acceleration, respectively^{7,8,19,21,22,31,42}. For higher frequencies of head motion that are still within the linear amplitude range, the neuronal responses increasingly lead the stimulus waveform, with irregular afferents reaching phase leads of greater than 90 deg (that is, approximately one-quarter of the stimulus waveform)^{7,8,19,21,22,31,42}. Additionally, both canal and otolith afferents demonstrate high-pass tuning such that neuronal response sensitivities increase with the frequency of head motion stimulation (reviewed in REF.⁵⁴). The left panel of part a of the figure shows the population-averaged sensitivities and phase leads of canal afferent responses to head angular velocity as a function of frequency⁵. In everyday life, however, head movements reach much higher rotational velocities and translational accelerations than those typically applied in experimental studies of the vestibular system^{6,23–25}. The middle panel of part a of the figure shows the approximate range of rotational velocities typically tested in neurophysiological studies relative to the rotational head velocities generated during natural activities in monkeys and humans^{6,23,24}. Recent

analyses of canal afferent responses to naturalistic self-motion have revealed that regular afferents transmit more information through firing rate, whereas irregular canal afferents demonstrate significant nonlinearities and transmit more information via a precise spike-timing code⁷ (see the right panel of part a of the figure). Asterisks indicate statistical significance at the *P*=0.05 level. Specifically, regular afferents transmit more information about head motion than irregular afferents through changes in firing rate (compare the normalized mutual information (MI) for each type of afferent). By contrast, irregular afferents are better able to discriminate between head motion stimuli through differential patterns of precise (~6 ms) spike timing than their regular counterparts.

Correlated activity between pairs of irregular afferents (but not single-afferent activity) can also provide detailed information about the envelope of the head motion stimulus⁹. The left panel of part b of the figure shows the time-varying head motion waveform (known as the carrier and a first-order component of the signal) for which the amplitude (the envelope, a second-order component of the signal) varies more slowly. The right panel of part b shows how the correlated activity of a pair of irregular afferents provides detailed information about this second-order feature of vestibular input. Part a is adapted with permission from REF.⁵, American Physiological Society, and REF.⁷, Springer Nature Limited. Part b is adapted with permission from REF.⁹, Proceedings of the National Academy of Sciences.



intensities that are an order larger than those typically applied in laboratory recording experiments. For example, it has been shown that the range of rotational horizontal head movement velocities generated by a monkey during natural behaviour reaches values $>1,500 \text{ deg s}^{-1}$ (REF.²⁴) (BOX 1). In addition, analysis of the frequency composition of natural motion stimuli (known as the power spectrum) has revealed that these stimuli contain a substantial proportion of components at high frequencies (which may be up to 20 Hz). Interestingly, the power spectrum of natural visual and auditory stimuli can be fit with a straight line when plotted in coordinates of log power versus log frequency (for review, see REF.²⁶). This relationship, referred to as a power law distribution, indicates that the stimuli show scale invariance (for example, at a given scale, a natural visual scene has a statistical structure that is invariant to any change in that scale). By contrast, natural vestibular stimuli do not follow a power law distribution^{23,24}. Instead, both active motion and the passive biomechanical filtering that occurs before any neural processing influence the structure of the natural vestibular stimuli detected by the vestibular sensory organs²³.

Dual coding strategies. This new knowledge of the statistics of natural vestibular stimuli suggests that vestibular processing is not amenable to analysis with linear models and has obvious implications for our understanding of how early vestibular pathways actually represent the stimuli encountered in everyday life.

In response to the high-amplitude stimuli generated during natural behaviours, it has been shown that afferents will exhibit standard neural nonlinear features, including a cut-off for large movements in the off direction (because their firing rate cannot be negative) and saturation for large movements in the on direction (when their firing rate reaches its maximum)⁶. For this reason, the well-established linear models of early vestibular processing described above are valid only over an extremely restricted range of movements and cannot predict responses over a full range of behaviours (including running, jumping and climbing). Instead, it has been suggested that linear–nonlinear cascade models are required. These comprise two stages: a linear system representing the high-pass tuning of a neuron followed by a simple scalar nonlinearity, such as a sigmoid, to represent neuronal cut-off and saturation⁶.

In addition, the results of recent studies have provided insight into the ways in which vestibular afferent coding is constrained by the statistics of natural self-motion stimuli. In particular, they indicate that irregular otolith and canal afferents are better optimized to process natural stimuli than regular afferents because their optimal stimulus distributions more closely match the natural stimulus distribution¹⁰. Interestingly, it has been proposed that type I hair cells (which tend to supply irregular afferents (FIG. 1a)) evolved as an adaptation to the transition from water to a land-based environment (for review, see REFS^{27–29}). The geometry, tuning and timing of the afferent synapses onto type I hair cells in mammals are consistent with the facilitation of fast and reliable transmission to central pathways to ensure

stable gaze and posture on land³⁰. Thus, the neural coding strategies used by the vestibular system appear to have evolved to match the statistics of natural stimuli.

Finally, these findings can help to address one of the key questions that arose from the analyses described above: if irregular afferents are more sensitive to head motion than their regular counterparts and better optimized for encoding natural vestibular stimuli, why do we have regular vestibular afferents? Recent experiments have established that regular canal afferents transmit twice as much information via rate coding over the physiologically relevant range of head movements and have significantly lower detection thresholds than their irregular counterparts^{5,31}. By contrast, irregular canal afferents have a greater capacity to discriminate between different stimulus waveforms by generating differential patterns of precise spike timing on a timescale of 6 ms (REF.⁷). A preliminary report suggests that irregular otolith afferents similarly display precise spike timing⁸.

Current evidence therefore supports the idea that there are two parallel and distinct peripheral sensory channels representing vestibular information in mammals (BOX 1): one channel that represents the detailed time course of small-amplitude stimuli through firing rate and another that is better optimized for the natural range of head motion and uses a nonlinear code (precise spike timing). Interestingly, irregular otolith afferents are exceptionally sensitive to head motion and are likely to display synchronized population firing in response to dynamic stimulation^{8,9,32}. It has been proposed that this synchronous response can be assessed by measuring short-latency linear vestibular sensory evoked potentials (VsEPs), which are produced in response to transient linear acceleration of the head³³. Specifically, the activity of irregular otolith afferents dynamically leads acceleration, thereby encoding its mathematical derivative — jerk. In turn, measured VsEPs depend on jerk intensity³³. Accordingly, VsEPs have become an increasingly popular tool for assessing otolith function following genetic manipulation in rodents and may prove useful as a clinical test of otolith function (reviewed in REF.³⁴).

Implications for central vestibular coding. There are reasons to believe that the two parallel streams of sensory input provided by regular and irregular afferents are preserved and further refined in mammalian central vestibular pathways. First, it has been hypothesized that regular afferents may predominately target a second primary subclass of neurons in the vestibular nuclei. These neurons are termed position-vestibular-pause (PVP) neurons because they respond to eye position and pause their firing during saccades in addition to responding to vestibular stimulation (FIG. 2a; reviewed in REF.⁴). PVP neurons project to the extraocular motor neurons that control the eye muscles to generate the VOR, which stabilizes gaze by driving eye movements in the opposite direction to ongoing head motion. The ability of the VOR to accurately stabilize gaze over a wide range of head movements encountered in everyday life^{35,36} suggests that it receives input encoding the detailed time course of the head motion stimulus, which is consistent with the information being transmitted by regular afferents.

Precise spike timing

A situation in which information is encoded by the precise timing of the action potential sequence generated by a neuron.

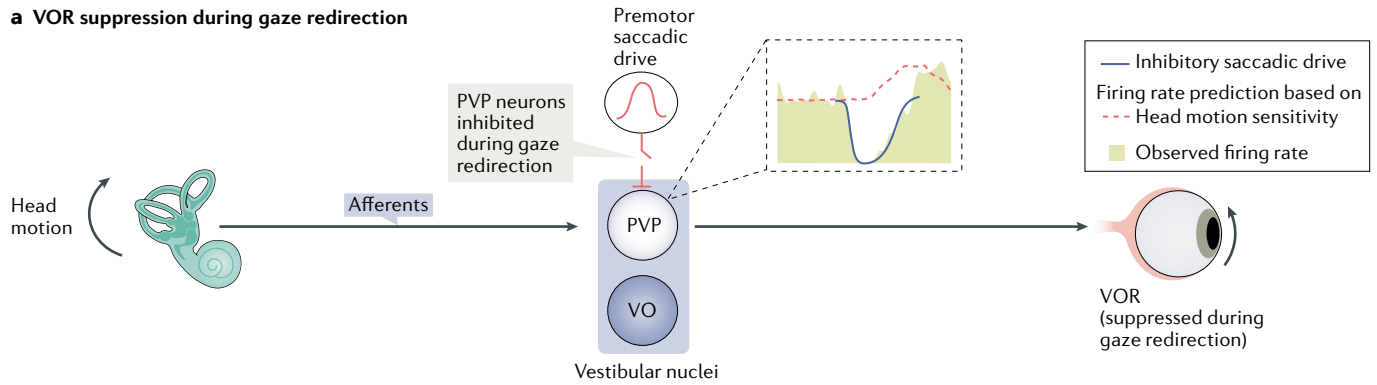
Jerk

The rate of change in acceleration, which mathematically is the first derivative of acceleration.

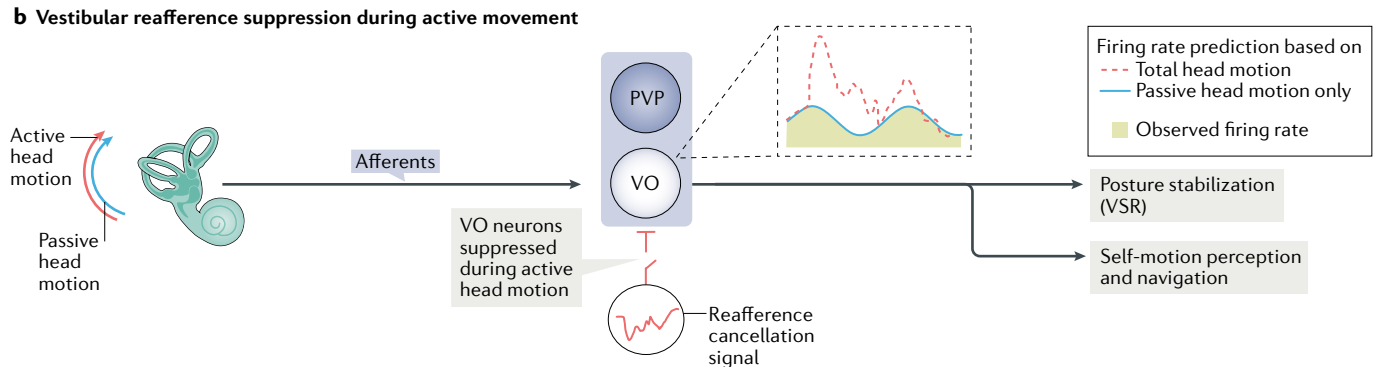
Saccades

Rapid movements of the eyes made to voluntarily shift the axis of gaze between fixation points.

a VOR suppression during gaze redirection



b Vestibular reafference suppression during active movement



c Theoretical framework for computation of vestibular reafference cancellation signal

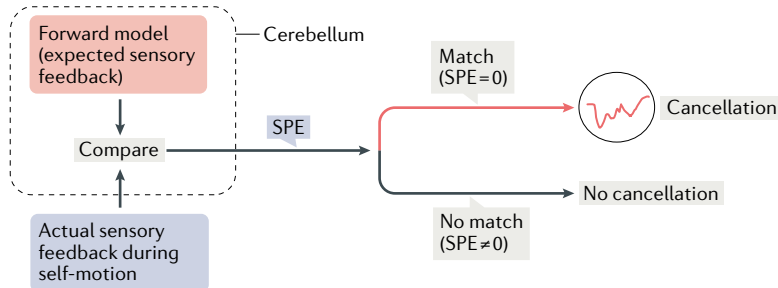


Fig. 2 | Motor and multisensory integration in the vestibular nuclei.

Whereas vestibular afferents encode head movements regardless of the behavioural goal, the responses of central neurons mediating the vestibulo-ocular reflex (VOR) and of those projecting to vestibulo-spinal (ascending) pathways are differentially modulated by extravestibular information. **a** | The schematic illustrates the pathway that mediates the VOR reflex, which acts to stabilize gaze in response to head motion. When the goal of the head movement is to voluntarily redirect gaze, the responses of central VOR neurons are suppressed. Specifically, the responses of the position-vestibular-pause (PVP) neurons that mediate the intermediate link in the VOR pathway are strongly inhibited by input from the premotor saccadic pathway that drives gaze shifts via its direct projections to extraocular motor neurons¹⁴. This inhibition is denoted on the schematic as a ‘gate’ that closes when the goal is to voluntarily redirect (rather than stabilize) gaze. The inset illustrates the reduced firing rate of a PVP neuron during a voluntary gaze shift relative to a firing rate prediction based on its sensitivity to the same type of head motion during the VOR¹⁴. The inhibitory saccadic drive can be accounted for by known brainstem mechanisms. Specifically, burst neurons in the brainstem paramedian pontine reticular formation generate a burst of spikes to drive horizontal saccadic eye movements and send direct inhibitory projections to the vestibular nuclei^{198,199}. **b** | The schematic illustrates the vestibulo-spinal pathways that mediate postural stabilization through the vestibulo-spinal reflex (VSR), self-motion perception and navigation. Within this pathway, vestibular-only (VO) neurons respond to passive head motion.

However, when the behavioural goal is to generate active head motion, the responses of central VO neurons are suppressed. Specifically, VO neurons receive a strong inhibitory cancellation signal when there is a match between the expected sensory consequence of the neck motor command and the actual neck proprioceptive feedback. Such a match functions to cancel vestibular reafference and suppress VO neuron responses^{10,15,16}. Inset illustrates the firing rate response of a VO neuron during combined active and passive head motion. In this condition, monkeys generated active head-on-body movements (red arrow) while being passively rotated by the vestibular turntable (blue arrow), such that head motion is the sum of the passive sinusoidal stimulus and the monkey’s active head movement. The inset illustrates the selective cancellation of the VO neuron’s response to the active component of the head motion. Specifically, the neuron responds to the passive sinusoidal component of the head motion stimulus (superimposed blue trace) but is unresponsive to the active component of head motion. The dashed red trace shows the firing rate prediction based on total head motion¹⁶. **c** | Schematic illustrating the generation of the reafference cancellation signal that suppresses VO neuron activity in the cerebellum. During active movement, the brain computes an internal (forward) model of the expected sensory consequences of a motor command. This estimate is compared with the actual sensory inflow to compute the sensory prediction error (SPE). When there is match between the expected and actual sensory inflow (that is, SPE=0), vestibular reafference is suppressed^{15–17}. Inset in part **a** is adapted with permission from REF.¹⁴, Springer Nature Limited. Inset in part **b** is adapted with permission from REF.¹⁶, American Physiological Society.

Boosting nonlinearity

A nonlinearity characterized by lower sensitivities to lower-amplitude than to higher-amplitude head motion, which is observed when high-frequency and low-frequency head motion stimuli are simultaneously applied.

On the other hand, irregular afferents predominantly (but not exclusively) project to a subclass of neurons in the vestibular nuclei that, in turn, project to the spinal cord, vestibular cerebellum and thalamus^{37,38}. These neurons contribute to the vestibulo-spinal reflexes that ensure the maintenance of posture and accurate control of balance^{39–41}. They are called vestibular-only (VO) neurons because they are insensitive to eye movements (FIG. 2b; reviewed in REFS^{4,13}). Recent work has established that VO neurons, similar to irregular afferents, display spike-timing precision⁷ as well as an intrinsic boosting nonlinearity for high-frequency stimulation that accentuates the representation of transient movements⁴². These findings suggest that VO neurons transmit a highly nonlinear neural representation of self-motion to targets in the spinal cord, cerebellum and thalamus to ensure the maintenance of posture and accurate self-motion perception.

The coding strategies used by early vestibular pathways are likely to have important implications for higher levels of processing. Notably, sensory perception across many sensory systems is commonly thought to follow Weber's law, which states that discrimination thresholds increase proportionally with increases in the physical intensity of the stimulus⁴³. This feature of sensory coding is thought to be a consequence of the scale invariance of natural stimuli and the adaptation of coding strategies to such scale invariance^{26,44,45}. However, as noted above, natural vestibular stimuli have a unique structure²³, and there is indeed evidence that vestibular perception deviates from Weber's law — at least for rotational stimuli⁴⁶ (but see REF.⁴⁷ for translational stimuli).

Furthermore, vestibular perceptual and reflexive responses appear to be regulated by the envelope of self-motion^{48,49} (BOX 1). Observed across sensory stimuli, the envelope is a second-order stimulus attribute that is related to variance in the stimulus over time, describing, for example, changes in visual contrast or modulations in auditory amplitude. The envelopes of natural vestibular signals have recently been characterized in humans⁴⁸, and studies in monkeys have revealed that correlated neural activity across the vestibular afferent population encodes envelope information⁹. Although their functional role is not yet fully established, vestibular envelopes may have significant clinical relevance. For example, there is emerging evidence that envelopes are important in the central processing of vestibular input and that abnormalities in their coding contribute to vertigo susceptibility in patients with vestibular migraine^{49,50}.

Translational implications. The recent advances in our understanding of the coding strategies used by early vestibular pathways may also have direct translational impact. Human clinical trials of a vestibular implant that replaces semicircular canal function in patients with vestibular sensory loss with a multichannel 3D gyro-based vestibular prosthesis are currently ongoing⁵¹. Notably, the mapping between head motion and nerve stimulation in these devices is based on a linear–nonlinear cascade model describing afferent responses to motion^{6,21}.

In the future, taking into account more recently discovered features of sensory coding (such as spike-timing precision) is likely to contribute to further optimizing the performance of such devices to treat the serious problem of vestibular loss.

Early extr vestibular integration

Self-motion cues are provided not only by the vestibular sensory organs but also by other sensory systems, including the visual, proprioceptive and somatosensory systems. For example, motion of the visual world across the retina (commonly termed optic flow) is capable of generating powerful sensations of motion even when a subject is motionless. Consider the experience of sitting on a stationary train and looking out the window as the neighbouring train suddenly pulls away from the station. The resultant visual motion induces a strong yet false perception of self-motion. Furthermore, much (if not most) of the vestibular input we experience during our lives is actually the result of our own voluntary behaviour. Although such active behaviours stimulate the vestibular sensors, they also activate proprioceptors within the muscles that generate them and somatosensory receptors in skin surrounding the moving joints^{52,53}. In addition to the rich convergence of these extr vestibular sensory inputs, premotor signals related to the generation of eye and head movements are also relayed to early vestibular pathways. Thus, the question of where and how the brain integrates vestibular and extr vestibular cues is essential for understanding how the brain computes its estimate of self-motion. Recent findings indicate that, in mammals, some multisensory and motor signals are combined at early stages of vestibular processing — a feature of this sensory system that has important implications for understanding the cortical representation of self-motion — whereas other integration does not take place until higher levels of processing. Additionally, following peripheral vestibular loss, the substitution of extr vestibular sensory and motor information in early vestibular pathways contributes to improvements in gaze stability and balance (BOX 2).

Subcortical multimodal sensory integration. In response to visual optic flow, PVP neurons at the first central stage of mammalian vestibular processing encode premotor signals related to the generation of eye movements. Notably, optic flow stimulation produces reflexive optokinetic eye movements that supplement the VOR to stabilize gaze during low-frequency head motion (reviewed in REF.⁵⁴). Thus, PVP neurons contribute to the stabilization of gaze by simultaneously driving eye movements produced by both the VOR and optokinetic reflexes.

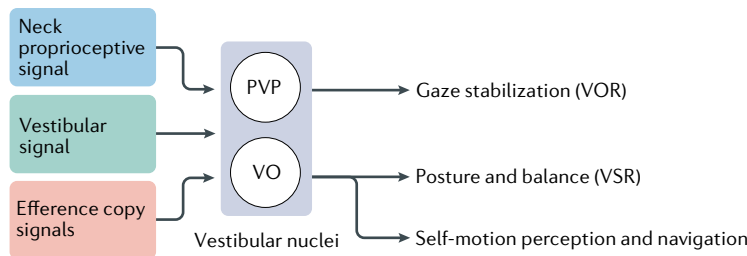
For many years, it was thought that visual self-motion cues also strongly drive the activity of VO neurons, which in turn send ascending projections to the vestibular thalamus to mediate self-motion perception. According to this view, the interaction of visual and vestibular information in VO neurons can explain the powerful sensations of self-motion we can experience even when motionless. However, although there have been reports

Box 2 | **Peripheral vestibular loss: sensory versus motor substitution**

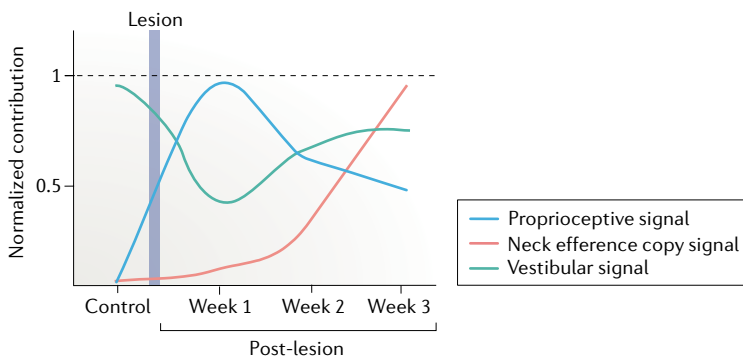
Patients with peripheral vestibular loss initially display severe symptoms that include head tilt, involuntary spontaneous nystagmus eye movements and a deficient vestibulo-ocular reflex (VOR). These symptoms typically show substantial improvement within a month of the injury that caused the vestibular loss^{1,172}. Changes in the intrinsic properties of vestibular nuclei neurons (such as their spontaneous activity, basic excitability and resonance) in the absence of synaptic stimulation (reviewed in REF.¹⁷³), as well as changes in the strength of commissural connections between left and right vestibular nuclei^{174,175}, are thought to contribute to this compensation. Indeed, changes in commissural connectivity can generate nearly instantaneous compensatory changes in the synaptic efficacy of both VOR and vestibulo-spinal reflex (VSR) pathways^{176,177}.

A substantive contribution to compensation following peripheral vestibular loss is also mediated by the unmasking of extravestibular inputs at the level of the vestibular nuclei^{178–180} (see the figure, part a). Specifically, single-unit recording studies in rhesus monkeys have revealed that, within 24 h of vestibular loss, both position-vestibular-pause (PVP) and vestibular-only (VO) vestibular nuclei neurons show robust responses to passive stimulation of neck proprioceptors that are not present before the lesion, consistent with the rapid unmasking of inputs that are normally silent^{178,179}. Furthermore, over the next several weeks, PVP and VO neurons display increasingly enhanced responses to active versus passive head movements owing to the unmasking of a second extravestibular input that transmits a motor efference copy signal^{178–180} (see the figure, part b). Extravestibular sensory and motor substitution following peripheral vestibular loss provides a concrete neural substrate for improvements in self-motion perception following vestibular loss¹⁸¹ and for the efficacy of vestibular rehabilitation programmes that focus on the importance of sensory reweighting as soon as possible after vestibular loss^{182,183}. Part b is republished with permission of the Society for Neuroscience, from *Neural correlates of motor learning in the vestibulo-ocular reflex: dynamic regulation of multimodal integration in the macaque vestibular system*, Sadeghi, S. G. et al. **30**, 10158–10168, 2010; permission conveyed through Copyright Clearance Center, Inc. (REF.¹⁷⁸).

a Sensory-motor integration in the vestibular nuclei



b Sensory and motor substitution following vestibular loss



of vestibular nuclei neurons demonstrating responses to optokinetic and vestibular stimulation (particularly for lower-frequency motion)^{55–58}, the extent of visual–vestibular convergence in the vestibular nuclei is now known to be far less than was initially assumed^{59–61}. Instead, as discussed below, visual–vestibular convergence predominantly occurs at subsequent levels of processing (in the vestibular cerebellum, thalamus and cortex).

During voluntary self-motion, mammalian vestibular pathways also integrate vestibular and proprioceptive information from the muscles and joints to ensure the accurate control of posture and balance. Notably, the convergence of vestibular and neck proprioceptive input is required to ensure that compensatory vestibulo-spinal reflexes account for the current position of the head relative to the neck^{62–64}. This integration occurs at the first central stage of vestibular processing (the vestibular nuclei) in many species, including mice⁶⁴, cats⁶⁵, squirrel monkeys⁶⁶ and cynomolgus monkeys⁶⁷. In rhesus monkeys, however, these inputs are integrated only at the subsequent levels of vestibular processing, most notably in the deep nuclei of the cerebellum^{10,11} and the vestibular thalamus¹².

Finally, it is important to note that our self-motion is generally not restricted to one dimension but rather comprises both rotational and translational motion that simultaneously stimulate receptors in the semicircular canals and otoliths. It has been shown that most neurons in the vestibular nuclei subadditively combine canal and otolith afferent information with a weighting that is frequency-dependent⁶⁸. Specifically, canal inputs are more heavily weighted at low frequencies and the weighting of otolith inputs increases with frequency. These findings are consistent with the results of psychophysical experiments showing that human subjects more accurately perceived angular displacement than linear displacement⁶⁹. The neural mechanisms underlying the integration of vestibular (that is, semicircular canal and otolith) and extravestibular (for example, visual, proprioceptive and motor) information at higher levels of the vestibular processing are further discussed below.

Integration of voluntary motor commands. Vestibular afferents encode head movements in the same manner irrespective of the current behavioural goal (reviewed in REFS^{4,18}). By contrast, a major hallmark of the next stage of processing in the mammalian vestibular nuclei is the integration of motor signals with vestibular information and the subsequent modification of that information. Recent studies have focused on two of the main motor-related inputs to the vestibular nuclei: eye movement (gaze) motor commands and head movement commands.

As reviewed above, PVP neurons comprise the middle stage of the three-neuron VOR pathway (FIG. 2a). The simplicity of this pathway leads to the generation of compensatory eye movements within ~5 ms of a head movement, stabilizing gaze over the range of head velocities and frequencies experienced in everyday life³⁵. However, in some situations the VOR is counterproductive. Notably, when the goal is to redirect (not stabilize) gaze using coordinated eye and head movements, an unmodified VOR would drive the eye in the direction opposite of the intended goal. In fact, in this situation, the gain of the VOR is significantly attenuated¹³ because the modulation of PVP neurons is suppressed during such gaze shifts¹⁴. This gaze-dependent gating of the VOR is mediated by inhibitory inputs from the brainstem premotor saccadic and pursuit pathways (FIG. 2a).

As outlined above, a different class of neurons in the vestibular nuclei — VO neurons — mediate the vestibulo-spinal reflexes and project to ascending thalamocortical pathways (FIG. 2b). Whereas VO neurons respond robustly to passively applied motion, their responses are markedly reduced (exhibiting ~70% suppression) when the same motion is actively generated^{10,15}. This observation is true both for head rotations^{10,15} and translations¹¹ as well as for multidimensional head movements². Moreover, these neurons can selectively encode passive self-motion even when this occurs at the same time as active self-motion, indicating the specificity of the gating by active motion signals^{10,16} (FIG. 2b). However, recent studies have revealed that a reafferent cancellation signal (FIG. 2b) suppresses actively generated vestibular input only when the actual sensory signal matches the brain's internal estimate of the expected sensory consequences of active movement^{16,17} (FIG. 2c). As discussed below, a cerebellar-based mechanism appears to compute the reafferent cancellation signal required for the preferential encoding of passively applied vestibular input by these neurons.

In summary, the coding strategy of VO neurons is fundamentally distinct from that of PVP neurons. PVP neurons robustly encode head velocity when the goal is to stabilize gaze; the efficacy of this reflex pathway is suppressed only when the goal is to voluntarily redirect gaze. On the other hand, VO neurons robustly and selectively encode externally applied (rather than self-generated) head motion; the efficacy of these neurons is suppressed when the goal is to voluntarily move the head relative to space.

Internal models of self-motion

The mammalian cerebellum integrates information from multiple sensory systems with motor commands and sends projections to premotor and motor areas of the cerebral cortex as well as brainstem nuclei and the spinal cord. It is notable that numerous regions of the cerebellum receive input directly from vestibular afferents (such as the nodulus and ventral uvula, the vermis (lobules I, II and VII) and the deep cerebellar nuclei) and/or from the vestibular nuclei (such as the flocculus and ventral paraflocculus) (reviewed in REF.⁵⁴). These regions of the vestibular cerebellum also receive other sensory-related signals (including visual, proprioceptive and somatosensory signals) in addition to motor-related inputs.

A prevailing view is that the cerebellum generates a forward internal model that predicts the sensory consequences of self-generated movement (reviewed in REF.⁷⁰). By comparing the difference between the actual and predicted consequences of a given motor behaviour, the cerebellum is thought to compute an error signal that drives the recalibration of motor centres. Furthermore, the cerebellum is thought to combine input from sensory systems to construct an integrated forward model of the expected sensory consequences of behaviour. There have been a number of attempts to model the brain's ability to combine inputs to compute spatial orientation and self-motion during passive and active movements. These theoretical studies have largely involved the implementation of mathematical

models that are based on adaptive filters, including the Smith predictor and the Kalman filter^{71–77}. Although such theoretical models are computationally powerful, it has been argued that direct biological implementation of many such engineering-based control architectures is implausible^{78,79}. Accordingly, the following discussion will focus on recent neurophysiological experiments in the vestibular cerebellum that have advanced our understanding of the computations that are performed in the cerebellum for the maintenance of posture, the generation of voluntary self-motion and the generation of the brain's internal estimate of gravity.

Frames of reference. Our everyday activities require that sensory information encoded in one reference frame (the set of axes used to describe an object's position or motion) be transformed into another to generate appropriate behaviour. For example, because the vestibular receptor organs are located in the inner ear, the vestibular system's native reference frame is head centred. However, to enable accurate motor control and ensure that sensory perception remains stable, the brain must often combine vestibular signals with other sensory information in order to transform it into a reference frame that is relevant to ongoing behaviour.

The generation of vestibulo-spinal reflexes requires that central vestibular pathways explicitly transform vestibular information from a head-centred to a body-centred reference frame. Experiments in rhesus monkeys have shown that the vestibular nerve and vestibular nuclei, similar to the vestibular receptor organs, encode vestibular inputs in a head-centred reference frame^{10,11,14–16,21,80,81}. By contrast, vestibular-sensitive neurons in the rostral portion of the most medial of the deep cerebellar nuclei, the fastigial nucleus (rFN), can represent self-motion signals in a body-centred reference frame. This property was initially demonstrated for 2D motion constrained to the horizontal plane^{82,83} and has been recently shown to fully generalize to three dimensions⁸⁴.

This transformation requires the integration of neck proprioceptive signals with vestibular signals, such that the motion of the head in space can be compared with the motion of the head relative to the body in order to compute body motion (FIG. 3a). Thus, proprioceptive input from the neck shapes vestibulo-spinal reflexes so that the resultant corrective movements are able to offset changes in the position of the head relative to the body^{62,63,85}. Likewise, the convergence of vestibular and proprioceptive inputs underlies the ability of human subjects to perceive body motion independently of head motion⁸⁶. The rFN receives input from regions of the vestibular cerebellum that include the cerebellar vermis (lobules I–V), where neurons encode vestibular and neck proprioceptive-related signals during passive self-motion (reviewed in REF.⁵⁴). In turn, rFN neurons encode passive head-in-space versus body-in-space motion in two distinct streams⁸⁷. Bimodal rFN neurons display comparable (and antagonistic) responses to passive vestibular and proprioceptive stimulation and effectively encode body-in-space motion⁸⁷ during passive stimulation protocols. Unimodal rFN neurons,

Reafferent cancellation signal

A signal computed by the brain to cancel the sensory consequences of actively generated vestibular stimulation produced during voluntary movements.

Adaptive filters

Filters with parameters that can be adjusted to learn, and in turn attenuate, the transmission of predictable features of the input.

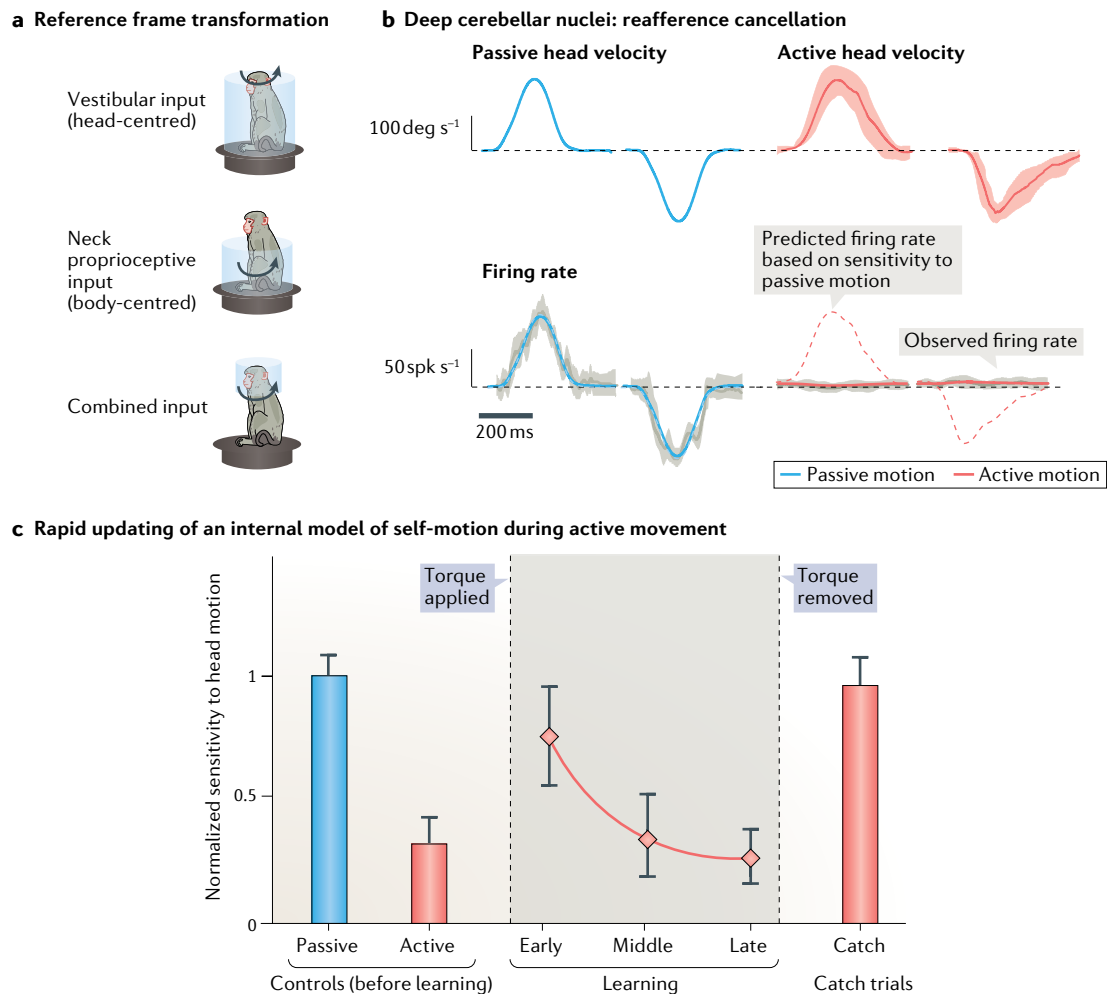


Fig. 3 | Internal models of self-motion in the vestibular cerebellum. a | Schematic demonstrating stimulation of the vestibular (head-centred) and proprioceptive (body-centred) systems in a monkey. The vestibular system alone is stimulated by passively rotating the head and body together relative to space (whole-body rotation; top panel) and the proprioceptive system alone is stimulated by passively rotating the body under the head, which remains stationary (middle panel). By contrast, passive rotation of the head relative to the body (bottom panel) produces combined stimulation of the proprioceptive and vestibular systems, thereby allowing us to investigate the transformation of vestibular input from head-centred to body-centred coordinates. **b** | The responses of an example deep cerebellar nuclei neuron during passive and active (voluntary) motion paradigms. The top traces illustrate head velocity, the bottom traces show neuronal firing rate responses and the dashed red line indicates a prediction of the firing rate in the active condition based on the neuron’s sensitivity to passive motion. The neurons show robust modulation by passive motion, but their responses are minimal when the same motion is actively generated. In the lower panels, grey shading corresponds to the average firing rates and standard deviations for the same ten movements²⁰⁰. Overlaying blue and red lines show the average firing rate responses to passive versus active motion, respectively²⁰⁰. **c** | When the relationship between the head motor command and resultant movement is altered by applying a resistive load (torque), neuronal vestibular sensitivities to head motion during active head movements initially increase to levels measured during passive head motion. They then gradually decrease to those measured during active head motion before torque application. Once the brain’s internal model has been updated to accommodate the new relationship between the voluntary head motor command and the resultant movement, neuronal sensitivities during active trials in which the load is removed (catch trials) are comparable to the neuronal sensitivity during passive head movements¹⁷. Notably, the re-emergence of afferent suppression during learning, represented by a decrease in the normalized sensitivity of neuronal responses, follows the same time course as the corresponding change in head movement error (not shown)¹⁷. Part **b** is adapted with permission from REF.²⁰⁰, Elsevier. Part **c** is adapted from REF.¹⁷, Springer Nature Limited.

on the other hand, respond only to passive vestibular inputs and thus encode passive head-in-space motion. Notably, the vestibular and proprioceptive responses of bimodal neurons display comparable tuning (that is, the strength and location of maximal response is similar), and in both cases this tuning varies as a nonlinear

function of head-on-body position⁸⁷. The complementary tuning for these two modalities underlies the ability of bimodal rFN neurons to robustly encode body motion.

The results of lesion experiments provide causal evidence that the integration of neck proprioceptive signals with vestibular signals in the rFN is vital for postural

control (reviewed in REF.⁵⁴). It is also noteworthy that evidence for a transformation from head-centred to body-centred coding is evident at even earlier stages of vestibular processing for other mammalian species. Specifically, a substantial percentage of neurons at the first central stage of processing (the vestibular nuclei) in cats, alert squirrel monkeys and cynomolgus (*Macaca fascicularis*) monkeys respond to both passive vestibular and proprioceptive stimulation^{88,89}. Indeed, in mice, most vestibular nuclei neurons display vestibular–neck proprioceptive convergence⁶⁴.

Internal models of active self-motion. It has long been appreciated that the brain must distinguish sensory stimuli that are the result of self-generated (that is, active) stimulation from those that are the result of passive stimulation to ensure perceptual stability⁹⁰. The ability to distinguish sensory reafference from exafference is also vital for ensuring accurate motor control. Consider that, in the vestibular system, the same central neurons receiving direct afferent input also send direct projections to motor centres to control vestibulo-spinal reflexes. As outlined above, vestibulo-spinal reflexes are essential for providing a robust postural response to unexpected vestibular stimuli but are counterproductive when the goal is to make active head movements. Thus it is logically beneficial to suppress these reflex pathways during active movements. As reviewed above, VO neurons preferentially code vestibular exafference at the first central stage of vestibular processing in a number of species^{10,15,64,66,67}. Specifically, VO neuron responses to vestibular stimulation are suppressed when there is a match between the brain's motor-based prediction (internal model) of expected sensory input and the actual sensory feedback that is experienced (for review, see REFS^{4,18}), as would be the case during normal voluntary self-motion.

There are many reasons to believe that the vestibular cerebellum plays a central role in generating the required cancellation signal. First, deep cerebellar nuclei neurons (such as rFN neurons) robustly encode passive self-motion, but their responses to active self-motion are markedly attenuated¹⁷ (FIG. 3b). Furthermore, during a paradigm in which monkeys learn to adapt their active head movements to compensate for an applied load, rFN responses dynamically track the difference between predicted and actual sensory feedback¹⁷. Trial-by-trial analysis during this learning revealed that neuronal response sensitivities to vestibular input subsequently decline with the same time course as the concurrent behavioural learning (FIG. 3c), thereby providing a neural correlate for the rapid updating of an internal model that enables the motor system to learn to expect unexpected sensory inputs. In this context, the responses of rFN neurons provide evidence for the output of a cerebellar computation that calculates a sensory prediction error to ensure both the distinction between actively generated and passively applied vestibular inputs (FIG. 2c) and the calibration of motor circuits to ensure accurate motor performance when sensory errors become persistent (as would be the case as muscles fatigue or change in strength over time). In turn, the deep cerebellar nuclei neurons of the rFN project to the VO neurons of the

vestibular nuclei, which similarly reflect the updating of the forward model predicting the sensory consequences of head motion¹⁷. This modulation of vestibulo-spinal reflex pathways serves a vital role by selectively encoding a continuously updated representation of unexpected motion, thereby ensuring the control of posture and maintenance of balance.

Thus, during active movement, inputs from the semicircular canal and otolith organs (reafference) are cancelled by a cerebellum-based mechanism that compares the actual sensory feedback experienced with that predicted by the brain's internal model of the sensory consequences of its actions. In theoretical studies, an internal model of the sensory consequences of active self-motion has been realized^{69,76,91} as a Kalman filter incorporating both motor commands and sensory information for self-motion estimation in active and passive conditions. Interestingly, there is support for the idea that the cerebellum plays a role in generating the cancellation signal required to suppress sensory reafference in other systems^{92,93}. Thus, it is likely that the cerebellum-mediated suppression of self-generated sensory reafference is a common strategy across species and sensory systems. Future studies exploring the cerebellum will be needed to develop experimentally motivated circuit models of the mechanisms by which the brain actually computes an internal model of self-generated sensory reafference.

Internal models of spatial orientation. The mammalian vestibular cerebellum also has an important role in the computations underlying the brain's ability to estimate our orientation relative to gravity. Otolith afferents encode inertial stimuli generated during translational self-motion and changes in head orientation relative to gravity in an identical manner. Einstein's equivalence principle⁹⁴ posits that these inputs are physically indistinguishable from one another, meaning that the otolith afferents transmit ambiguous information to the brain (reviewed in REF.⁹⁵). Importantly, however, changes in head orientation relative to gravity also stimulate the semicircular canals. Thus, the brain can integrate information from the otolith and canal afferents to distinguish between these two movement conditions^{96–99}.

Another way to think about this is that the integration of otolith and canal signals underlies the transformation from a head-centred to a gravity-centred reference frame, such that a distinct estimate of the orientation of the head relative to space is computed. Indeed, Purkinje cells in the nodulus and ventral uvula (lobules X and IX) of the vestibular cerebellum in monkeys integrate otolith and semicircular canal inputs. Whereas some of these Purkinje cells preferentially encode passive translation^{100–102}, others appear to better encode applied head tilts relative to gravity^{98,103}. Consistent with the computation of gravity-referenced coding, lesions of the nodulus and/or uvula produce deficits in the gravity-dependent processing of vestibular information for reflex behaviours in monkeys^{104,105}. Moreover, a recent study in rodents reported that Purkinje cells in the same cerebellar region predominantly encode changes in head orientation relative to gravity rather than translations²⁵.

Interestingly, the authors speculate that these neurons might be less responsive to active stimulation than to passive stimulation during locomotion. A recent preliminary experimental report in monkeys suggests that, indeed, the internal model that enables the distinction between passive and active motion (FIG. 2c) also takes into account the influence of gravity¹⁰⁶.

Self-motion perception

In addition to ensuring gaze and postural stability, the mammalian vestibular system plays a vital role in essential cognitive functions, including the accurate perception of self-movement and orientation. For instance, healthy human subjects can discriminate the direction of rotational whole-body motion at velocities that are below 1 deg s^{-1} in darkness^{14,107,108}, whereas the threshold velocities that can be discriminated by patients with complete bilateral vestibular loss are an order of magnitude higher¹⁰⁹. Experiments in monkeys have likewise shown a tenfold decrease in the ability to discriminate the direction of a translational heading following bilateral vestibular loss¹¹⁰.

At the early stages of vestibular processing, the sensitivity of individual afferents and vestibular nuclei neurons to whole-body motion is substantially lower than that observed during tests of perception^{22,31}. Although an earlier study reported otolith afferent sensitivity of the same order of magnitude as behaviour¹¹¹, the analysis approach significantly underestimated these values by not taking into account the cosine dependency of the tuning curves of individual otolith afferents (for discussion, see REF.22). Moreover, the abilities of vestibular nuclei neurons to detect whole-body motion are actually even worse than those of their afferent inputs^{5,22,31} (FIG. 4). Similar results have also been reported for otolith and vestibular nuclei neurons recorded during a perceptual task^{112–115}. These results suggest that ascending vestibular pathways must integrate information from large populations of vestibular nuclei neurons to obtain perceptual performance levels (FIG. 4a). Furthermore, the fact that pooling across multiple afferents results in worse (rather than better) detection thresholds at the level of the vestibular nuclei suggests that early vestibular pathways have adapted a nonlinear processing strategy to extract particular features from self-motion. For instance, vestibular afferents project directly to VO neurons in the vestibular nuclei, which demonstrate a static boosting nonlinearity in their input–output relationship that accentuates the representation of high-frequency stimuli^{7,42}.

How do downstream neurons in the thalamus decode the information from the vestibular nuclei to generate the perception of self-motion? Vestibular information is transmitted to the cortex via two thalamocortical pathways — one anterior and one posterior. The anterior vestibulo-thalamocortical pathway originates in the vestibular nuclei and targets the anterior dorsal thalamus, which in turn projects to the entorhinal cortex and presubiculum (FIG. 1b). This pathway constitutes the head direction (HD) cell network (reviewed in REF.116), which plays an essential role in generating the sense of heading required for navigation^{117,118} and

is considered in detail below. By contrast, the posterior vestibulo-thalamocortical pathway is thought to underlie the precise coordination of self-motion perception and action (reviewed in REF.119). Previous studies have demonstrated that neurons in the vestibular posterior lateral thalamus display even more pronounced nonlinearities than VO neurons in the vestibular nuclei neurons in response to passively applied vestibular stimulation^{12,37} and are characterized by response gains that decrease markedly with increasing stimulus amplitude. To date, whether this nonlinear processing is also consistent with a precise spike-timing code remains an open question.

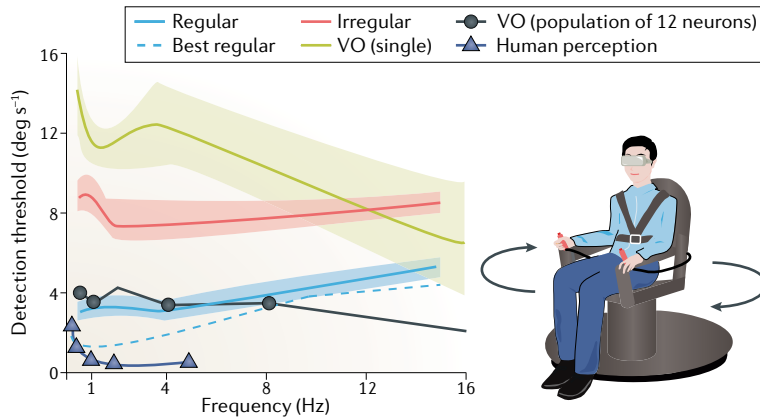
Multisensory integration at higher stages of vestibular processing

The deep cerebellar nuclei and the vestibular nuclei send ascending projections to the ventral posterior lateral thalamus, which is also the main somatosensory nucleus of the thalamus (reviewed in REF.120). Neurons in this thalamic nucleus are multimodal; they encode both vestibular signals and information provided by other inputs, including somatosensory, proprioceptive and/or visual sensory information and motor signals^{121–123}. The ventral posterior lateral thalamus in turn relays information to analogously multisensory regions of the cortex, which are vital for the construction of our perceptual estimate of head and body motion relative to space (FIG. 4b). In particular, areas that receive direct input include the parieto-insular vestibular cortex (area PIVC), the ventral intraparietal area (area VIP), area 2v of the intraparietal sulcus and area 3a in the sulcus centralis (reviewed in REFS^{54,120}). In addition, neurons in other areas, such as the medial superior temporal area (area MST) respond to vestibular stimulation in the dark (reviewed in REFS^{54,120}). Accordingly, and in contrast to the visual and auditory systems, no specific region of the cortex is specifically dedicated to vestibular processing. Each of these areas appears to serve a distinct but complementary role in the integration of multisensory information and motor signals for self-motion perception and control of voluntary movement.

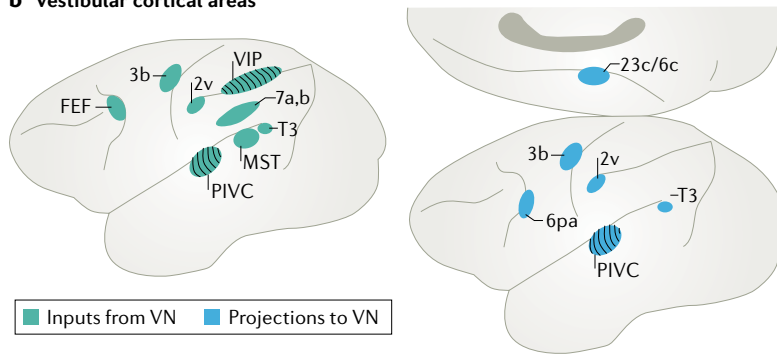
Area PIVC is thought to play a central role in the cortical vestibular network. This cortical area is strongly interconnected with somatosensory cortex areas 3a and 2v¹²⁴. Stimulation of area PIVC in patients produces vestibular sensations¹²⁵, whereas lesions of this area impair orientation perception¹²⁶. Electrophysiological studies have shown that area PIVC neurons are the site of a rich convergence of multisensory cues including vestibular stimulation, full-field optokinetic stimulation, somatosensory stimulation and/or stimulation of proprioceptive receptors in the neck and (occasionally) limbs^{124,127–129}. Furthermore, during a passive heading discrimination task, reversible lesions of this region increased psychophysical heading detection thresholds¹³⁰. Interestingly, because area PIVC neurons also respond robustly to external visual target motion, it has been proposed that this area effectively monitors the motion of the head and/or body motion relative to external space during self-motion^{124,131,132}.

Neurons in cortical area VIP also demonstrate extensive multisensory integration. In darkness, area VIP

a Neural versus perceptual detection thresholds



b Vestibular cortical areas



c Relative sensitivity to active self-motion

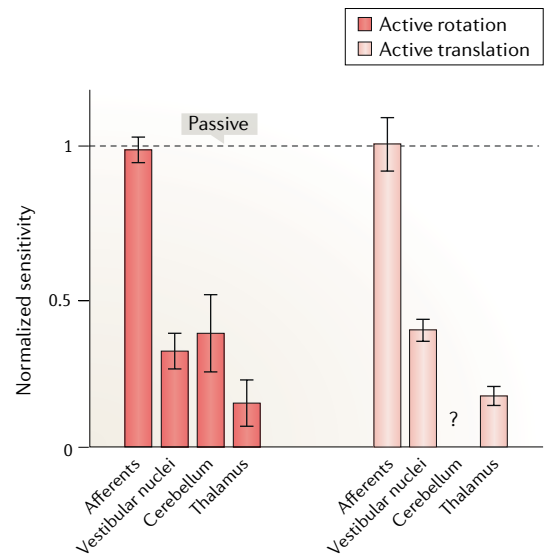


Fig. 4 | Vestibular processing for self-motion perception. a | A comparison of the average behavioural and neuronal thresholds for the detection of whole-body motion. The results of psychophysical studies in humans in which subjects experienced applied whole-body rotation in darkness around an Earth vertical axis (as illustrated to the right) at different frequencies are shown. Superimposed for comparison are the neuronal detection thresholds (\pm s.e.m.) measured in alert monkeys for populations of regular and irregular semicircular canal afferents as well as central vestibular-only (VO) neurons. The neuronal detection threshold computed for a pooled population of 12 VO neurons is also shown, assuming independent noise. Notably, in order to recover the level of information required to explain psychophysical performance, ascending vestibular pathways must integrate information from large populations of vestibular nuclei (VN) neurons. Psychophysical and neuronal data from REF.¹⁰⁸ and REF.⁵ respectively. **b** | A schematic drawing illustrating the regions of cortex that receive inputs from the VN (left panel) and those that project back to the VN (right panel)¹²⁹. Striped regions denote areas that receive direct input from the VN. **c** | Comparison of neuronal responses to active rotations and translations (normalized relative to responses to comparable passive motion; dashed line) at four successive stages of vestibular processing: the vestibular afferents (data from REFS^{21,151}), the VN (data from REFS^{10,11}), the fastigial nucleus in the cerebellum (data from REF.²⁰⁰) and the thalamus (data from REF.¹²). Note that neurons at each subsequent stage of central vestibular processing are increasingly selective to passive self-motion (vestibular exafference). Error bars show s.e.m. FEF, frontal eye field; MST, medial superior temporal area; PIVC, parieto-insular vestibular cortex area; VIP, ventral intraparietal area. Part **a** is adapted with permission from REF.⁴, Elsevier. Part **b** is adapted with permission from REF.¹²⁹, Wiley-VCH. Part **c** is adapted from Dale, A. & Cullen, K. E. The ventral posterior lateral thalamus preferentially encodes externally applied versus active movement: implications for self-motion perception. *Cereb. Cortex* **29**, 305–318, by permission of Oxford University Press (REF.¹²).

neurons respond to passively applied whole-body rotations and translations^{133–135}. Additionally, single area VIP neurons are often responsive to applied somatosensory and/or proprioceptive stimulation^{136,137} and to full-field visual information^{138,139}. Importantly, the vestibular responses of area VIP neurons are generally stronger than their optic flow responses and are significantly correlated with behavioural responses during a passive vestibular heading discrimination task¹⁴⁰. Moreover, the responses of area VIP neurons do not vary as a function of either eye or head position¹⁴¹, consistent with the view that these neurons encode a representation of heading direction relative to the world. Somewhat surprisingly, however, a recent study reported that inactivation of area

VIP does not produce perceptual deficits in heading discrimination tasks¹³⁰. Further work will be required to fully understand this apparent paradox.

Finally, area MST, a region of extrastriate cortex long known to play a role in visual motion and self-motion perception based on optic flow, has also been well studied regarding its role in combining vestibular and visual information^{142–145}. Notably, neurons in the dorsal region of area MST (MSTd) can respond to both optic flow and vestibular stimulation^{142,146}. Furthermore, some area MSTd neurons combine these inputs in a manner that is consistent with the improvement that is observed in behavioural heading detection thresholds when both cues are present (reviewed in REFS^{147,148}), and inactivation

Continuous ring attractor network

A recurrent network schematized as a ring of neurons around which moves a 'bump' of activity that indicates the current estimate of head direction.

of area MSTd worsens these behavioural thresholds¹⁴⁹. Ongoing work is currently focused on understanding the contribution of area MSTd to heading perception in the context of other cortical areas that also encode both visual and vestibular information, including the posterior portion of the area PIVC (the visual posterior sylvian area) and the smooth pursuit area of the frontal eye fields (reviewed in REF.¹⁵⁰).

Perception of active versus passive self-motion. As reviewed above, the brain distinguishes between vestibular information that is the result of externally generated (passive) versus voluntarily generated (active) movements at the first central stage of sensory processing (FIG. 2b). This distinction is likely to be vital for stable perception. To directly address whether this is the case, a recent study investigated how voluntary self-motion is represented in the posterior thalamocortical vestibular pathway (FIG. 1b). Consistent with the proposal that distinction between active and passive self-motion in early vestibular pathways contributes to perceptual stability, single-unit recordings in monkeys revealed that individual neurons in the ventral posterior lateral thalamus preferentially encode passive vestibular information, even when passive self-motion is experienced concurrently with active self-motion¹².

Overall, a hierarchical trend appears across the successive stages of processing in vestibular pathways — primary vestibular afferents respond robustly and equally to active and passive self-motion^{21,151} whereas neurons at each subsequent stage of central processing demonstrate increasing selectivity in their responses to passive self-motion (FIG. 4c). The following question then arises: how do neurons in vestibular-driven regions of the cortex encode active self-motion? To date, only two experimental neurophysiological studies have directly addressed this question. The first¹⁵² found that area VIP neuronal responses are usually attenuated for active

self-motion, consistent with the preferential transmission of passive vestibular information from the thalamus¹². By contrast, the second study¹³² reported that area PIVC neurons respond well to both active and passive head motion. However, as noted by the authors, it is likely that area PIVC neurons may have encoded a representation of self-motion relative to a specific visual target that was present in this study. Accordingly, future experiments are required to fully understand how different self-motion and environmental cues are integrated in the vestibular cortex to achieve perceptual stability during voluntary behaviours.

Sense of direction

Being able to form a picture of where we are going relative to where we have been requires us to know both where we are now and our orientation. In everyday life, this ability depends on the integration of both environmental cues and self-motion cues. Whereas the posterior thalamocortical vestibular pathway (discussed above) targets cortical areas including areas PIVC and VIP, the anterior thalamocortical vestibular pathway projects to the anterior dorsal thalamus and then on to the retrosplenial cortex and entorhinal cortex (via the presubiculum and parasubiculum; FIG. 1b). The latter pathway is thought to underlie the computations required to provide our sense of direction and spatial cognition during navigation (reviewed in REF.¹⁵³). Consistent with this idea, clinical studies have provided evidence linking vestibular loss to spatial cognitive disorders, including deficits in spatial memory and navigation (BOX 3).

The vestibular system and head direction. Single-unit recording studies in rodents have identified HD cells at multiple stages along the anterior thalamocortical vestibular pathway (reviewed in REF.¹¹⁶). HD neurons discharge in relation to the animal's directional heading in the horizontal plane, independent of the animal's location and behaviour^{154,155}, and recent functional MRI studies in humans have reported an HD signal in the human retrosplenial cortex¹⁵⁶. The prevailing view is that a continuous ring attractor network, which receives information on angular head velocity from the vestibular system, computes the HD signal (reviewed in REF.¹⁵⁷). A feature of this proposal is that, during self-motion, input from the horizontal semicircular canal initiates activity in the network. In turn, the network then integrates the input signal to produce a sustained representation of head position so that, as the head rotates between different directional headings in the environment during navigation, the locus of activity moves around the network's ring, thereby encoding different directional headings.

At first glance, the vestibular signal appears to be an ideal candidate for an input to the HD network. Lesions targeting sensory input from the vestibular semicircular canals disrupt directional tuning in HD cells (reviewed in REF.¹⁵⁸). Moreover, optogenetic inhibition of the nucleus prepositus, which receives input from the vestibular nuclei and projects to the HD circuitry, results in disruption of the HD signal and decreased performance in a homing task in rats¹⁵⁹. However, early vestibular pathways also integrate multimodal information. Notably, gaze and

Box 3 | Cognitive aspects of vestibular disorders

The hippocampus is thought to play a critical role in spatial navigation. It is activated when rodents navigate in a real environment and when rodents or human subjects navigate in a virtual environment^{184,185}. There are many reasons to believe that the vestibular system contributes to this function. First, caloric stimulation of the vestibular system activates the hippocampus¹⁸⁶. In addition, chronic bilateral loss of vestibular function leads to hippocampal atrophy, which correlates with impairments in spatial memory tasks¹⁸⁷. Hippocampal size, in turn, positively correlates with performance during navigation and spatial memory tasks^{188,189}. Furthermore, the hippocampus is one of the first regions to degenerate during the course of Alzheimer disease¹⁹⁰, and postural imbalance, as well as spatial disorientation and wandering, are common features of the disease^{191,192}.

Together, these findings have led to the recent proposal that there may be a direct link between peripheral vestibular loss and cognitive decline in patients with Alzheimer disease^{193,194}. Although there is no explicit evidence for a causal role, a recent study demonstrated that patients with cognitive impairment have poorer vestibular function (in particular impaired otolith responses) relative to age-matched controls¹⁹⁴. It is also noteworthy that the vestibular system has a widespread influence on cortical networks, which overlap areas disrupted in patients with Alzheimer disease¹⁹⁵. More generally, vestibular loss occurs with ageing and may be linked to cognitive decline in elderly individuals^{196,197}. Further probing the links between peripheral vestibular loss and cognitive impairment in disease, as well as in normal ageing, will be an essential direction for basic and clinical future research.

head motor efference copies, as well as vestibular signals, are encoded at the first central stage of processing. As reviewed above, in many species vestibular nuclei neurons also encode robust proprioceptive information^{64–67}. These results are consistent with reports that motor and proprioceptive influences can contribute to shaping the responses of HD cells^{160,161}. Thus, although the ascending anterior vestibulothalamic pathway is likely to be important for navigation, the question of precisely what information this pathway transmits for the computation of the HD signal during navigation remains open.

The HD network is also generally assumed to generate a fixed representation of perceived directional heading. Thus, the fact that vestibular nuclei neurons are suppressed during active head motion (FIG. 2b) further indicates that the computation must be dynamically updated to account for differences in vestibular input during active versus passive conditions^{162–164}. In addition, the brain's ability to calculate its sense of direction in different settings (for example, in the real world versus in an immersive video game) requires the learning of new and distinct relationships between sensory and motor cues so that it can effectively switch back and forth between states. Recent experiments controlling the correspondence between the intended and actual head movement during active movements have provided some insight into these computations^{16,17,164} (FIG. 3c). Notably, cerebellar circuits are updated to learn new matches when the expected correspondence between active head motion and the resultant sensory consequences is altered¹⁷. Thus, it has been proposed that the cerebellum plays a critical role in maintaining the stability of the HD network¹⁶⁴, an idea further supported by a recent modelling analysis¹⁶⁵. Indeed, there is recent experimental evidence that projections from the cerebellum to the HD cell network contribute to the construction of the hippocampal spatial representation map (mediated by place cells) during goal-directed navigation¹⁶⁶. However, further experiments will be required to understand the mechanisms that underlie the stable representation of directional heading in the HD circuit.

To date, higher-level representations of self-motion information during goal-directed navigation have been primarily studied in primates using virtual navigation tasks in which no actual vestibular cues or proprioceptive cues are present. During such virtual navigation tasks, area MST neurons can display enhanced directional responses to the current heading direction^{167,168}. It is noteworthy that during a 'voluntary driving' task in which trained monkeys steered a wheel to produce actual goal-directed head rotations, vestibular nuclei neurons respond robustly as if motion was passively applied^{10,169}. Although this driving task (unlike virtual navigation) did activate the vestibular system, it differs from natural navigation in that proprioceptive and motor-related signals that would normally be present during natural orienting movements and locomotion are absent (see REF.¹⁶⁴ for discussion). Overall, further work will be required to elucidate how the brain combines different task-related motor commands (such as those driving head turns, navigation and steering) with self-motion sensory feedback information (including

vestibular, proprioceptive and visual signals) during real, virtual and manually controlled (for example, driving a car or piloting a plane or space vehicle) navigation.

Conclusions

Major recent advances have substantially furthered our understanding of the function of the vestibular system during natural behaviours. Early vestibular pathways encode self-motion in a linear manner only when tested over a highly restricted range of amplitudes and frequencies, during which stimulation is passively applied. More generally, however, in everyday life the representation of self-motion by early vestibular pathways is strongly nonlinear. Notably, vestibular afferents as well as their target neurons in the central pathways mediating balance and perception utilize nonlinear coding strategies, including precise spike timing, to represent the stimuli encountered during everyday activities. Furthermore, the information transmitted by neurons at the first central stage of vestibular processing is regulated in a behaviour-dependent manner. In particular, in everyday life our vestibular systems are most often activated during voluntary behaviours rather than during passively applied self-motion. Recent work has shown that during such voluntary behaviours, the integration of multimodal sensory and motor information at the first stage of central vestibular processing profoundly shapes processing for subsequent stages of processing in the descending and ascending and vestibular pathways that control action and perception.

Several open questions remain regarding the computations that the brain performs on vestibular information to ensure stable perception and accurate motor control. First, how newly discovered features of early vestibular sensory coding, such as spike-timing precision, are decoded by downstream neurons in the thalamus and cortex to better optimize behavioural and perceptual performance is unknown. Second, the source of the vestibular cancellation signal that eliminates actively generated signals from early vestibular pathways has not yet been determined. Several converging lines of evidence indicate that the cerebellar cortex plays an essential role in computing the mismatch between expected and actual vestibular input required to compute a cancellation signal (FIG. 3c). However, further studies of the cerebellar cortex during active versus passive self-motion are needed to establish the neural mechanisms underlying this computation. In addition, it is likely that cancellation is hierarchically organized and that circuits in other CNS structures, including the HD circuit and the sensorimotor cortex, contribute to ensuring perceptual stability during active self-motion. Future experiments focused on how vestibular self-motion and environmental cues are integrated in these higher order areas during active real-world versus virtual-world behaviours will ultimately be fundamental to understanding the relation between sensory prediction and perceptual stability.

This Review traced vestibular processing from the periphery to the vestibular nuclei to the cortex, focusing on how motor signals play an essential role in gating out vestibular signals that are a consequence of active motion. However, it is important to consider that

activation of the vestibular systems produces behavioural responses, which will, in turn, influence voluntary behaviour. This then leads us to question where the motor signals originate during natural behaviours and what specific role cortically coded self-motion plays. Can new insights be gained by considering vestibular processing in the context of dynamically coupled bidirectional networks (as described in REFS^{170,171}) rather than through the traditional analysis of bottom-up perceptual and top-down motor pathways? The use of new recording technologies to study neural populations at different stages of vestibular processing across

such different behavioural contexts is likely to prove important to advancing our knowledge of the networks and neural computations underlying our perception of self-motion and ability to establish whether vestibular stimulation is self-produced or externally generated. Further probing the coding strategies used by this essential sensory system during natural behaviours also holds promise for understanding the mechanisms underlying the cognitive aspects of disorders linked to impairments of vestibular function (BOX 3).

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