J Neurophysiol 91: 1919–1933, 2004;
10.1152/jn.00988.2003.

Signal Processing in the Vestibular System During Active Versus Passive Head Movements

Kathleen E. Cullen and Jefferson E. Roy

Aerospace Medical Research Unit, Department of Physiology, McGill University, Montreal, Quebec H3G 1Y6, Canada

Submitted 14 October 2003; accepted in final form 9 January 2004

Cullen, Kathleen E. and Jefferson E. Roy. Signal processing in the vestibular system during active versus passive head movements. *J Neurophysiol* 91: 1919–1933, 2004; 10.1152/jn.00988.2003. In everyday life, vestibular receptors are activated by both self-generated and externally applied head movements. Traditionally, it has been assumed that the vestibular system reliably encodes head-in-space motion throughout our daily activities and that subsequent processing by upstream cerebellar and cortical pathways is required to transform this information into the reference frames required for voluntary behaviors. However, recent studies have radically changed the way we view the vestibular system. In particular, the results of recent single-unit studies in head-unrestrained monkeys have shown that the vestibular system provides the CNS with more than an estimate of head motion. This review first considers how head-in-space velocity is processed at the level of the vestibular afferents and vestibular nuclei during active versus passive head movements. While vestibular information appears to be similarly processed by vestibular afferents during passive and active motion, it is differentially processed at the level of the vestibular nuclei. For example, one class of neurons in vestibular nuclei, which receives direct inputs from semicircular canal afferents, is substantially less responsive to active head movements than to passively applied head rotations. The projection patterns of these neurons strongly suggest that they are involved in generating head-stabilization responses as well as shaping vestibular information for the computation of spatial orientation. In contrast, a second class of neurons in the vestibular nuclei that mediate the vestibuloocular reflex process vestibular information in a manner that depends principally on the subject's current gaze strategy rather than whether the head movement was self-generated or externally applied. The implications of these results are then discussed in relation to the status of vestibular reflexes (i.e., the vestibuloocular, vestibulocollic, and cervicoocular reflexes) and implications for higher-level processing of vestibular information during active head movements.

INTRODUCTION

The vestibular system is classically associated with detecting the motion of the *head-in-space* to generate the reflexes that are crucial for our daily activities, such as maintaining head and body posture (see Peterson and Richmond 1988) and stabilizing gaze during walking and running (Grossman et al. 1988, 1989). Angular head-in-space velocity is detected by vestibular hair cells that are located within the semicircular canals of the vestibular end organs (Goldberg and Fernández 1971). In turn, this information is relayed to neurons in the vestibular nuclei via the afferent fibers of the vestibular nerve. Single-unit experiments in head-restrained animals have shown that head-in-space velocity is reliably encoded at each of these sequential stages of processing during passive whole-body rotations (e.g., Cullen and McCrea 1993; Scudder and Fuchs 1992). However, in real life, the vestibular end organs not only inform the brain about the motion of the head during passively applied movements, but they are also simultaneously activated by vestibular stimulation arising from our own actions. To maintain postural and perceptual stability and to accurately guide behavior, the nervous system must differentiate between sensory signals that register changes in the external world and those signals that result from our own actions. For example, vestibulospinal reflex pathways play a critical role in controlling head and body posture by stabilizing the head and body relative to space. While these reflexes are crucial for compensating for externally applied head perturbations, they can be counterproductive when an animal decides to actively move its head and/or body relative to space.

Von Holst and Mittelstaedt (1950) originally put forth the hypothesis that the CNS differentiates between sensory signals that arise from our own actions and those that result from external events by sending a parallel "efference copy" of the motor command to sensory areas. In turn, this anticipatory signal is subtracted from the incoming sensory signal to selectively remove that portion due to the animal's own actions. In the vestibular system, an efferent pathway to the labyrinth has been described that could, in theory, underlie such a mechanism. Vestibular efferent somas are located in the periabducens region, and directly project via the VIIIth nerve to the vestibular hair cells in the labyrinth (Goldberg and Fernández 1980). It has been proposed that the primate efferent system functions to reduce the sensitivity of the vestibular nerve during voluntary head movements (Goldberg and Fernández 1980). Moreover, in addition to direct inputs from vestibular afferents, the vestibular nuclei receive substantial projections from cortical, cerebellar, and other brain stem structures. These structures could provide the vestibular nuclei with numerous extra-vestibular cues that could be used to dissociate between active and passive head rotations.

Here we review the results of recent experiments that have addressed the question: how does the nervous system differentiate between actively generated versus externally applied head movements? We focus on recent studies that have considered how head-movement information is encoded at the level of vestibular nerve afferents and neurons to which they project in the vestibular nuclei. First, the results of prior studies, which have characterized neuronal responses in head-restrained monkeys during passive whole-body rotations, are summarized. Next recent studies that have addressed the pos-

Address for reprint requests and other correspondence: K. E. Cullen, Aerospace Medical Research Unit, 3655 Promenade Sir William Osler, Montreal, Quebec H3G 1Y6, Canada (E-mail: kathleen.cullen@mcgill.ca).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

sible differential encoding of self-generated and passively applied rotations of the head-in-space are examined. Finally, the functional implications of the neurophysiological findings are discussed. In particular, we consider the status of vestibular reflexes during active and passive head movements as well as implications for higher-level processing of vestibular information.

VESTIBULAR AFFERENTS: ENCODING PASSIVE VERSUS ACTIVE HEAD MOTION

Passive head movements

The responses of vestibular afferents have been well characterized during passive head rotations. Vestibular afferents with more regular spontaneous firing rates closely encode angular head velocity over the frequency range of physiological head movements 2–20 Hz (Hullar and Minor 1999) with little change of sensitivity and a phase lead that increases with frequency. In contrast, vestibular afferents that have more irregular spontaneous firing rates demonstrate a gain enhancement and significant phase lead for frequencies above 10 Hz (Goldberg and Fernández 1971). It had been proposed (Minor and Goldberg 1991) that regular afferents might make the primary contribution to vestibuloocular reflex (VOR) pathway, which functions to stabilize the axis of gaze on the retina. In contrast, irregular afferents could be more useful in overcoming the load of the head and so might be involved in mediating the vestibulocollic reflex (VCR), which functions to stabilize gaze by generating compensatory head movements (Billito et al. 1982). However, a subsequent electrophysiological analysis of afferent inputs to secondary vestibulospinal and vestibuloocular neurons has indicated that both classes of afferents carry information to both groups of neurons (Boyle et al. 1992).

Active head movements

Does the vestibular system differentiate between active and passive head movements at the level of the vestibular afferents? The role of the efferent pathway to the labyrinth has been a long-standing mystery, but a popular hypothesis had been that it functions to increase resting discharge rate and reduce the rotational sensitivity of afferents during active head movements (Goldberg and Fernández 1980; Purcell and Perachio 2001). Thus efferent-mediated modulation would function to increase the dynamic range of afferent responses available for the encoding of active head movement. Experiments in barbiturate-anesthetized squirrel monkeys (Goldberg and Fernández 1980) and toadfish (Highstein 1992) had provided indirect support for this idea. In both studies, electrical stimulation of the vestibular efferent system resulted in a decrease in the sensitivity of the afferents to passively applied rotations. However, a more recent study, in which the responses of vestibular afferents during passive and active head movements were explicitly compared, is incompatible with this hypothesis (Cullen and Minor 2002). In alert head-unrestrained rhesus monkeys, the head-velocity sensitivities of canal afferents were comparable during passive and active head-on-body rotations. Importantly, this observation held for all classes of afferents: regularly, intermediate, and irregularly discharging afferents. Thus in the alert primate, the vestibular system does not appear to differentiate between active and passive head movements at the level of the vestibular afferents.

VESTIBULAR NUCLEI: ENCODING PASSIVE VERSUS ACTIVE HEAD MOTION

Overview

Does the vestibular system differentiate between active and passive head movements at the level of the vestibular nuclei? Although the processing of head movements by the vestibular nuclei has been well characterized during passive whole-body rotations, researchers have only recently begun to systematically explore vestibular processing during self-generated head movements. The processing of angular horizontal head velocity by the vestibular nuclei has been the most extensively characterized and hence is the primary focus of this review. The afferent fibers of the horizontal semicircular canals, which encode horizontal head velocity, project primarily to neurons within the rostral medial vestibular nuclei (rMVN) and the ventrolateral vestibular nuclei (vLVN) (Gacek and Lyon 1974). Single-unit recording experiments in alert head-restrained monkeys have shown neurons in these nuclei can be grouped into distinct classes based on idiosyncratic constellations of discharge properties during head-restrained eye movement paradigms and passive whole-body rotations (Chubb et al. 1984; Fuchs and Kimm 1975; Keller and Daniels 1975; Lisberger and Miles 1980; Miles 1974; Tomlinson and Robinson 1984). Of these, three principal classes receive direct inputs from the afferents: position-vestibular-pause (PVP) neurons, vestibular-only (VO) neurons, and eye/head (EH) neurons.

In addition to inputs from the vestibular afferents, the vestibular nuclei receive substantial projections from cortical, cerebellar, as well as numerous brain stem nuclei. These inputs could have important implications regarding the question posed in the preceding text because there are two key differences between active and passive head movements. During an active movement *1*) the CNS is aware that the head will move and thus should be able to predict the sensory consequences and *2*) the CNS has access to the motor command that is responsible for the movement of the head in space. Indeed, there are many routes by which either type of information could reach the vestibular nuclei.

First, the vestibular nuclei receive direct projections from cortical areas that have been implicated in the cognitive aspects of vestibular function including the perception of spatial orientation and the ability to navigate (for review, see Fukushima 1997). For example, the parieto-insular vestibular cortex (PIVC) sends a substantial projection to each of the vestibular nuclei (Akbarian et al. 1994). Inhibitory reciprocal interactions between visual cortical areas and the PIVC appear to be involved in the perception of verticality and self-motion (Brandt and Dieterich 1999; Deutschlander et al. 2002). Inputs from this area might encode signals representing the expected consequences of voluntary movements. However, the functional implications of the direct projections between cortical areas and the vestibular nuclei are not yet well understood.

Second, an internal copy of the motor command to drive the muscles (often termed motor efference copy signal) is also theoretically available to selectively modify the responses of

neurons in the vestibular nuclei during active movements. In particular, the vestibular nuclei receive direct inputs from structures, which could carry an efference copy signal including premotor neurons within oculomotor/gaze control pathways (Sasaki and Shimazu 1981), the vestibular cerebellum (Voogd et al. 1996), and the head/neck region of premotor cortical areas 6pa, 6c, and 23cv (for review, see Fukushima 1997). Projections from these structures could provide the vestibular nuclei with numerous extra-vestibular cues that could be used to dissociate between active and passive head rotations.

Additionally, it is important to note that signal processing in the vestibular nuclei has been traditionally tested by passively rotating the animals en bloc, such that the body, limbs, and head moved together in space. However, during active movements, this is not the case; the active motion of limbs, trunk, or neck muscles will activate proprioceptive inputs, which could in turn alter vestibular processing at the level of the vestibular nuclei. Thus there is a third critical difference between the information that is available to the vestibular nuclei during active head movements and head movements that have been passively applied in most prior characterizations of the vestibular nuclei. Indeed, there is substantial evidence from experiments in decerebrate animals to support the idea that activation of neck muscle spindle afferents influences the activity of vestibular nuclei neurons (Anastasopoulos and Mergner 1982; Boyle and Pompeiano 1980; Wilson et al. 1990). These inputs from neck muscle proprioceptors encode head-on-body motion signals that reach the vestibular nuclei via a disynaptic pathway mediated by the central cervical nucleus (Sato et al. 1997).

In summary, projections from cortical, cerebellar, and brain stem structures and neck proprioceptors converge within vestibular nuclei. However, until recently few studies had addressed how these multiple inputs were integrated during active head movements. Findings from recent studies have specifically addressed the question: do these inputs allow the vestibular system to differentiate between active and passive head movements at the level of the vestibular nuclei? This review will focus on recent work related to the three principal classes of second-order vestibular neurons, each of which mediates a specific functional role: PVP neurons are essential for the stabilization of gaze since they are an essential component of the pathways that mediate the VOR; VO neurons are thought to mediate the VCR and most likely also send projections to higher-order structures within the cerebellum and cortex; and EH neurons are the primary premotor input to the extraocular motoneurons during smooth pursuit and appear to make small contributions to the VOR and VCR pathways. These neurons send important direct projections to extraocular motoneurons as well as to areas of the brain stem and spinal cord involved in motor control. Hence, an unusual feature of the second-order neurons of the vestibular system is that they serve as both sensory and premotor neurons. In this way the vestibular system differs from most other sensory systems.

PVP neurons and the VOR

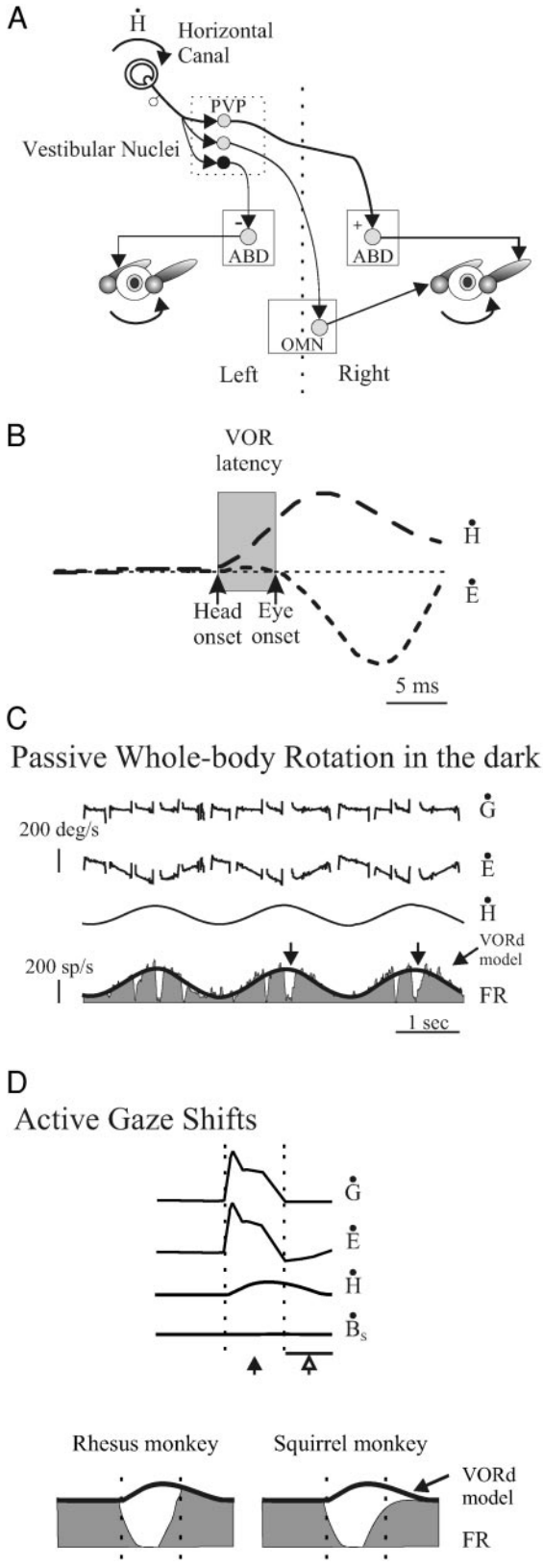
PASSIVE HEAD MOVEMENTS. The VOR is classically considered to be a stereotyped reflex, which effectively stabilizes gaze by moving the eye in the opposite direction to the applied head motion. The three-neuron arc responsible for mediating the VOR was first described by Lorente de No' in 1933. This pathway consists of projections from vestibular afferents to interneurons in the vestibular nuclei, which in turn project to extraocular motoneurons (Fig. 1*A*). The simplicity of this three-neuron arc is reflected in the fast response time of the VOR; compensatory eye movements lag head movements by only 5–6 ms in the primate (Fig. 1*B*) (Huterer and Cullen 2002; Minor et al. 1999). PVP neurons are thought to constitute most of the intermediate leg of the direct VOR pathway; they receive a strong monosynaptic connection from the ipsilateral semicircular canal afferents and project directly to the extraocular motoneurons (Cullen and McCrea 1993; Cullen et al. 1991; McCrea et al. 1987; Scudder and Fuchs 1992).

PVP neurons derive their name from the signals they carry during head-restrained head and eye-movement paradigms; their firing rate increases with contralaterally directed eye position; they are sensitive to ipsilaterally directed head velocity during passive whole-body rotations (Fig. 1*C*); and they stop firing or pause during ipsilaterally directed saccades and vestibular quick phases (denoted by arrows in Fig. 1*C*). The projections of PVP neurons to the extraocular motoneurons are consistent with their role in generating the VOR. The majority of PVP neurons send an excitatory projection to the motoneurons of the contralateral abducens nucleus (ABN; Fig. 1*A*) or medial rectus subdivision of the oculomotor nucleus (OMN; Fig. 1*A*). Only a minority sends inhibitory projections to the motoneurons of the ipsilateral ABN. Thus the signals sent by PVP neurons to the extraocular motoneurons result in the production of an eye movement in the opposite direction to head movement.

ACTIVE HEAD MOVEMENTS. Do PVP neurons (e.g., VOR interneurons) differentially process vestibular information during active versus passive head movements? Recent work has shown that PVP neurons process vestibular information in a manner that depends principally on the subject's current gaze strategy rather than whether the head movement was actively generated or passively applied. As summarized in the following text, the head-velocity signals carried by VOR pathways are reduced when the behavioral goal is to *redirect* the visual axis of gaze. In contrast, head-velocity signals encoded by PVP neurons are remarkably consistent when the behavioral goal is to *stabilize* the visual axis of gaze relative to space.

Gaze redirection. There is much accumulated evidence from studies in head-restrained monkeys to indicate that PVP neurons differentially encode head-velocity during gaze redirection versus gaze stabilization. First, although PVP neurons encode head velocity during the compensatory slow phase component of the VOR evoked by passive whole-body rotation, they pause or significantly decrease their firing during vestibular quick phases where gaze is redirected (Cullen and McCrea 1993; Fuchs and Kimm 1975; Keller and Daniels 1975; Keller and Kamath 1975; Lisberger et al. 1994a,b; McConville et al. 1996; McCrea et al. 1987; Miles 1974; Roy and Cullen 1998, 2002; Scudder and Fuchs 1992; Tomlinson and Robinson 1984). Second, these same studies have shown that PVP neurons pause when head-restrained monkeys redirect gaze by generating ocular saccades. Third, PVP neuron responses are attenuated by ~30% as compared with passive rotation in the dark when monkeys suppress their VOR (and therefore redirect their gaze to move with the head relative to

space) during passive whole-body rotation by tracking a target that moves with the head (Cullen and McCrea 1993; McCrea et al. 1996; Roy and Cullen 1998, 2002; Scudder and Fuchs 1992).



In more natural conditions, where the head is *not* restrained, a combination of rapid eye and head movements (a *gaze shift*; Fig. 1*D*, *top*, filled arrow) is commonly used to redirect the visual axis to a new target in space (reviewed in Guitton 1992). During gaze shifts, the eye movements produced by the VOR would be counterproductive; the VOR would produce an eye-movement command in the direction opposite to that of the intended shift of gaze. It was initially proposed that the VOR remained functional during gaze shifts, such that it eliminates the head's contribution to the change in gaze (Bizzi et al. 1971; Morasso et al. 1973). However, there is now substantial evidence that the VOR is not fully intact during gaze shifts (e.g., Fuller et al. 1983; Guitton and Volle 1987; Laurutis and Robinson 1986; Pélisson et al. 1988; Tabak et al. 1996; Tomlinson 1990; Tomlinson and Bahra 1986).

A neural correlate for this on-line suppression of the VOR response gain has been recently identified in monkey in a series of experiments (McCrea and Gdowski 2003; Roy and Cullen 1998, 2002) in which the responses of single PVP neurons were recorded. In these studies, neurons were first recorded in head-restrained behaving monkeys using "field standard" paradigms (i.e., saccades, smooth pursuit, and passive whole-body rotation). Once a neuron was fully characterized, the monkey's head was released, and the responses of the same neuron were recorded during large voluntary gaze shifts. For ipsilaterally directed gaze shifts, the head-velocity-related responses of PVP neurons were consistently attenuated relative to their response during the VOR elicited by whole-body rotation in the dark (Fig. 1*C*). This is shown in Fig. 1*D* in which a model based on the neuron's response during passive rotation in the dark (heavy line) systematically overpredicted each PVP neuron's response during gaze shifts. During large contralaterally directed gaze shifts (i.e., the off direction with respect to the neuron's head velocity sensitivity), PVP neurons were generally driven into cutoff.

A similar result was obtained in the analysis of PVP neuron discharges during *gaze pursuit* (Roy and Cullen 2002). As during gaze shifts, an intact VOR would also be counterproductive during gaze pursuit; it would generate an eye-movement signal in the direction opposite to that of the ongoing tracking. Indeed, when monkeys redirect their gaze by generating combined eye-head gaze pursuit, the head-velocity sensitivity of PVP neurons is significantly attenuated as compared

FIG. 1. Position-vestibular-pause neuron activity during passive and active head movements. *A*: schematic diagram of the direct vestibuloocular reflex (VOR) pathway. Rotation of the head to the left excites neurons in the left vestibular nuclei. Position-vestibular-pause (PVP) neurons send excitatory projections to motoneurons in the right abducens (ABN) and oculomotor nucleus (OMN) to generate right eye movements of both eyes. *B*: the latency of the eye movements evoked by the VOR is ~5 ms. *C*: discharge activity of a PVP neuron during passive whole-body rotation in the dark (VORd). Arrows, pauses during vestibular quick-phases. A model based on the head-movement sensitivity estimated during vestibular slow-phases is superimposed on the firing rate trace (VORd model; thick trace) *D*: a typical combined eye-head gaze shift in which the monkey voluntarily moved its head relative to its body (solid arrow). PVP neurons in rhesus and squirrel monkeys pause in activity at gaze shift onset and resume activity toward the end of the gaze shift. In rhesus monkey, PVP neuron activity in the post gaze shift period (open arrow) is well predicted by the VORd model. Similar results were found in squirrel monkey when a visual target was present; however, when the target was removed, neurons were less responsive than predicted by the VORd model (thick trace; see text for details). $\dot{E}$: eye-in-head velocity; $\dot{H}$: head velocity; $\dot{G}$: gaze velocity ($=\dot{E} + \dot{H}$); $\dot{B}_S$: body-in-space velocity; FR: firing rate.

with passive whole-body rotations (~50%). However, the attenuation was significantly less than that observed during large gaze shifts (e.g., 75% attenuation for 65° gaze shifts) (Roy and Cullen 2002).

Gaze stabilization. As was stated in the above text, an intact VOR may not be beneficial during active head movements when the behavioral goal is to redirect gaze to a new target. In contrast, a fully functional VOR is essential during active head movements when the behavioral goal is to maintain stable gaze. Interestingly, there have been reports that VOR gains in humans can be enhanced during active head-on-body rotations as compared with passive whole-body rotations (Demer et al. 1993; Jell et al. 1988). One possible explanation is that the CNS's knowledge of the active head movement is used to increase the modulation of VOR pathways in such conditions.

Roy and Cullen (2002) addressed the possibility that the head-velocity sensitivities of PVP neurons might be enhanced in conditions where a subject has knowledge of an intended head movement. Neuronal responses were compared during passive whole-body rotations and during self-generated movements of the head in space in a task where the monkey controlled its movement through space by manually operating a steering wheel. The head-velocity sensitivities of PVP neurons were identical in both cases, indicating that the knowledge of a self-generated head movement does not in itself modulate the responses of VOR pathways.

Experiments from two laboratories have addressed two additional possibilities, namely that information derived from either neck proprioceptive and/or neck motor efference copy signals is used to selectively modify the sensitivity of the VOR pathways during active head movements. Neuronal responses were compared during passive whole-body rotations and active head movements during periods of stable gaze. In particular, the analysis of active movements focused on the latter portion of the gaze shift, where the head continues to move, but the axis of gaze is stable relative to space (Fig. 1*D*, *top*, open arrow). In rhesus monkeys, PVP neurons similarly encoded head movement during these active head rotations and passive whole-body rotations (Fig. 1*D*) (Roy and Cullen 1998, 2002). Similarly, McCrea and Gdowski (2003) reported that in squirrel monkey responses were predicted by the neuron's sensitivity to passive-whole-body rotation when a visual target was present. However, they found that if a visual target was absent, neuronal discharges were less well related to head motion in the ipsilateral direction (e.g., Fig. 1*D*) but remained sensitive to head motion in the contralateral direction.

Results in rhesus monkey are consistent with accumulating evidence in human that VOR gains are generally comparable during passive and active rotations of the head-on-body (Foster et al. 1997; Hanson and Goebel 1998; Pulaski et al. 1981; Santina et al. 1999, 2000, 2002; Thurtell et al. 1999) as well as the finding that neither neck proprioceptors nor motor efference copy inputs alter VOR response dynamics in this primate species (Huterer and Cullen 2002). Results in squirrel monkey suggest that in this species VOR gain should be sensitive to reafferent sensory and motor inputs during active movements.

SUMMARY. Recent studies have shown that the head-velocity-related response of the direct VOR pathways is modulated in a manner that is consistent with the behavioral goal of the animal. The responses of activity of the primary VOR interneuron (PVP neurons) have been recorded during a diverse range of vestibular stimuli protocols including: passive whole-body rotation, passive head-on-body rotation, active eye-head gaze shifts, active eye-head gaze pursuit, self-generated whole-body motion (i.e., driving). Regardless of the stimulation condition, head-velocity-related modulation of PVP neurons is generally comparable whenever monkeys stabilized their gaze relative to space. In contrast, when the behavioral goal was to redirect gaze relative to space, PVP neuron responses to head motion are significantly reduced.

VO Neurons: VCR and higher-level vestibular processing

PASSIVE HEAD MOVEMENTS. In addition to its crucial role in stabilizing the eye relative to space via the VOR, the vestibular system also coordinates postural reflexes. Vestibular reflexes such as the 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 (Baker et al. 1985; Ezure et al. 1978; Goldberg and Peterson 1986; Peterson et al. 1981; Wilson et al. 1990).

VO neurons project to the cervical spinal cord and are thought to mediate the VCR pathway (Fig. 2*A*) (Boyle 1993; Boyle et al. 1996; Gdowski and McCrea 1999; Wilson et al. 1990). Like PVP neurons, VO neurons receive direct monosynaptic projections from vestibular nerve afferents and are sensitive to ipsilaterally directed head rotations during passive whole-body rotations. However, unlike PVP neurons they are insensitive to eye movements (Cullen and McCrea 1993; Scudder and Fuchs 1992) and do *not* play a role in mediating the VOR. Figure 2, *B* and *C*, shows the firing behavior of a typical VO neuron during passive whole-body rotation (*B*) and saccadic eye movements (*C*).

It is likely that VO neurons play a role in generating vestibulospinal reflexes, which control the excitability of forelimb and hindlimb, in addition to mediating the VCR; Single vestibulospinal neurons that project to the cervical spinal cord can have multiple axon collaterals that also project widely to other segments in the spinal cord (i.e., thoracic and lumbar) (Abzug et al. 1974; Shinoda et al. 1988). Moreover, VO neurons are thought to be interconnected with cerebellar structures that are involved in vestibular processing (e.g., nodulus-uvula, flocculus, and fastigial nucleus) as well as vestibular-related areas of the thalamus and cortex (see *What are the implications for vestibular- and neck-related reflexes?*). Thus VO neurons may also play a role in the higher-level processing of vestibular information. For example, the nodulus/uvula is involved in transforming head-referenced movement information into an inertial (gravity-referenced) coordinate frame (Angelaki and Hess 1995; Wearne et al. 1998), and it is likely that VO neurons are involved in this computation.

ACTIVE HEAD MOVEMENTS. As was the case for the VOR, vestibulospinal reflexes can be counterproductive during certain behaviors. For example during active head-on-body motion (gaze shifts and pursuit) the stabilization responses produced by the VCR would produce head-movement commands in the direction opposite to those of the intended self-generated motion. However, until quite recently, we

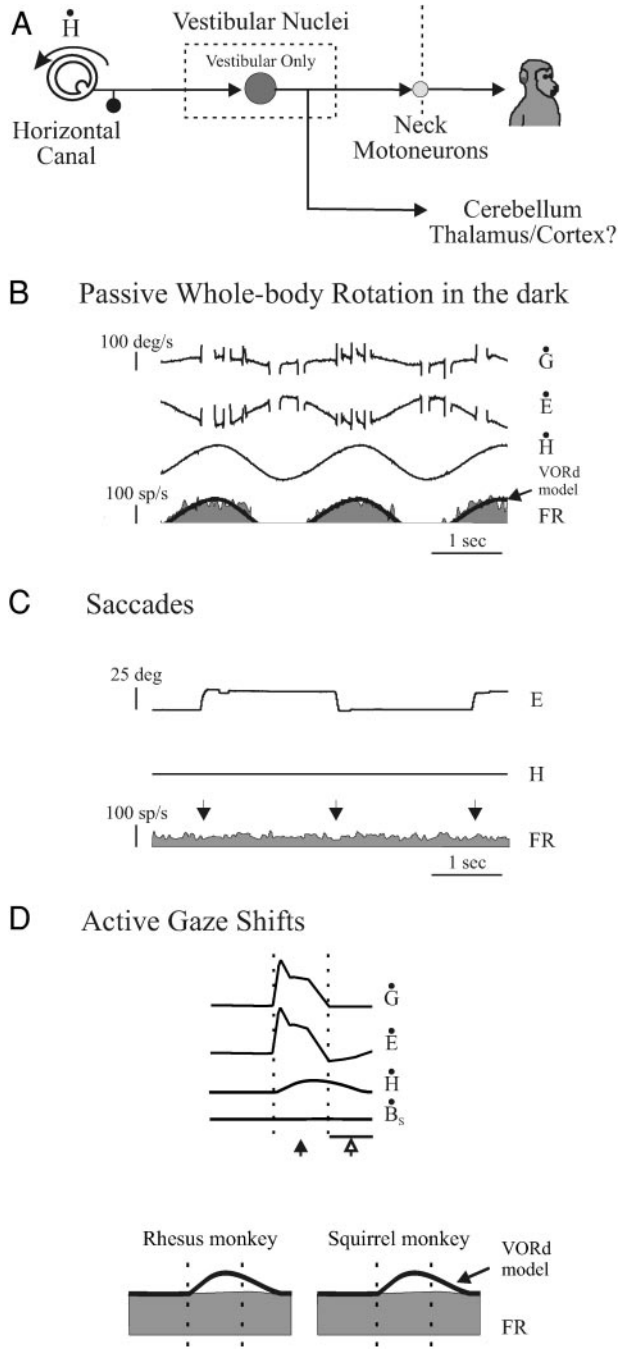


FIG. 2. Vestibular-only neuron activity during passive and active head movements. *A*: the vestibulocollic reflex (VCR) pathway is mediated at least in part by vestibular-only (VO) neurons in the vestibular nuclei. VO neurons receive direct projections from the semicircular canals and in turn project bilaterally to spinal motoneurons to activate the neck musculature. In addition, VO neurons most likely send projections to the cerebellum and may also directly project to the thalamus and cortex. *B*: discharge activity of a VO neuron during passive whole-body rotation in the dark (VORd). *C*: VO neurons are not responsive to changes in eye position or during saccades (↓). *D*: VO neuron responses to head motion in both species are attenuated during gaze shift (↑) and during the period immediately after where gaze is stable (xxx). A model based on estimated head-movement sensitivities during VORd (VORd model; —) overpredicts neuronal responses during both time intervals. E, eye position; H, head position.

had little knowledge of how head-velocity signals were processed by vestibulospinal pathways during active head movements. Indeed, most of our knowledge of vestibulospinal reflexes was derived from work in anesthetized animals using passive head rotations.

The first study of VO neurons in alert animals, during active head-on-body movements, suggested that neurons similarly encoded head-velocity signals during passive whole-body rotation and active head movements (Khalsa et al. 1987). However, considerable evidence from both rhesus (Cullen et al. 2001; Roy and Cullen 2001) and squirrel monkey (Boyle et al. 1996; McCrea et al. 1996, 1999) suggests that this is not the case. These more recent studies have shown that VO neurons are attenuated, on average, by about ~70% during the active head movements made during gaze shifts. In Fig. 2*D*, data are shown for a typical VO neuron. Note the response to head velocity is dramatically attenuated during gaze shifts as compared with passively applied head rotations (Fig. 2*B*). In contrast to PVP neurons, the head-movement sensitivity of VO neurons not only is attenuated during combined eye-head gaze shifts (Fig. 2*D;* filled arrow), but also immediately after gaze shifts when gaze is stable in space but the head is still moving (Fig. 2*D;* open arrow) (McCrea et al. 1999; Roy and Cullen 2001). Moreover, VO neurons show comparable attenuation for head movements made during different behaviors. For example, VO neuron responses are similarly attenuated for active head movements made during gaze shifts and gaze pursuit (Roy and Cullen 2001).

Interestingly, VO neurons continue to faithfully encode information about passive head rotations, which occur during the execution of voluntary movements. (McCrea et al. 1999; Roy and Cullen 2001). To date, considerable progress has been made in understanding the mechanism that enables VO neurons to selectively encode passive head rotation. First, it has been shown that knowledge of the self-generated head motion is not sufficient to modulate VO neuron responses. Neuronal activity was recorded while monkeys "drove" their own head and body motion together in space by rotating a steering wheel connected to the motor controller of a vestibular turntable (Roy and Cullen 2001). VO neurons responded robustly to head motion during this task; no significant attenuation was observed when compared with passive whole-body rotations. Second, studies have addressed whether the passive activation of neck proprioceptors might contribute to the suppression of vestibular-related responses in these neurons. In squirrel monkey, there is evidence in support of this proposal; VO neurons can be less sensitive to passive rotations of the head relative to the body than to passive rotations of the head and body together in space (Gdowski and McCrea 2000). However, comparable experiments in rhesus monkey generally found no difference in the modulation of VO neurons during these two types of passive stimulation (Roy and Cullen 2001). Similarly, passive activation of neck proprioceptors via rotation of the body beneath an earth stationary head does not affect neuronal responses in rhesus monkey (Roy and Cullen 2001) but can modulate neuronal responses in squirrel monkey (Gdowski and McCrea 2000; Gdowski et al. 2001).

Preliminary data in cynomolgus (*Macaca fascicularis*) monkey suggest that most VO neurons in this species of macaque monkey behave similarly to those of the rhesus monkey (*M. mulatta*) and are not sensitive to neck inputs (S. G. Sadeghi and K. E. Cullen, unpublished observation). Thus in macaque monkeys, an efference copy of the motor command to move the head is required for the differential processing of vestibular

information during active head movements (Roy and Cullen 2001). However, it is interesting that in cynomolgus monkeys a small percentage (~20%) of VO neurons is responsive to passive rotations of the body beneath an earth stationary head. This suggests that neck inputs may be slightly more important in this species of macaque. As compared with rhesus monkeys, cynomolgus monkeys are far more arboreal; they can spend as much as 97% of their time in trees (Wheatley 1980) and from a behavioral viewpoint are similar to squirrel monkeys who are also largely arboreal. Thus one possible explanation for the difference observed across species is that neck-related inputs to vestibular pathways are particularly critical for postural stabilization for those primates that make their home in a challenging three-dimensional environment.

SUMMARY. Recent studies have shown that the head-velocity related responses of VO neurons are selectively attenuated during active movements of the head relative to the body. To understand the mechanism that underlies this differential processing of vestibular information, VO neurons have been tested during a diverse range of vestibular stimuli protocols including: passive whole-body rotation, passive head-on-body rotation, active eye-head gaze shifts, active eye-head gaze pursuit, self-generated whole-body motion (i.e., driving). Overall, findings are consistent with the proposal that an efference copy of the neck motor command is required for the differential processing of active versus passive head-movement information at the level of the vestibular nuclei.

Eye-head neurons: pursuit pathways and vestibular reflexes

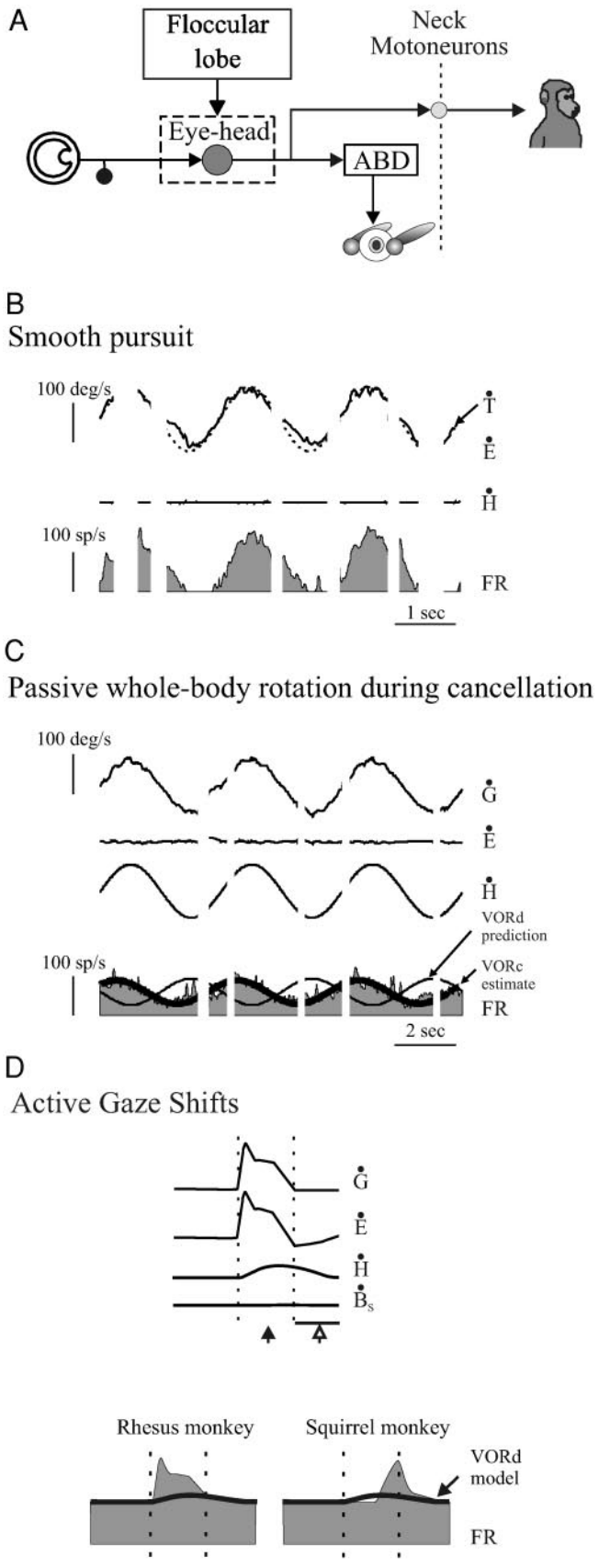
PASSIVE HEAD MOVEMENTS. Smooth pursuit is mediated, at least in part, by a cortico-ponto-cerebellar pathway arising from the medial superior temporal sulcus (MST) of extrastriate cortex. This pathway accesses the brain stem circuitry via inhibitory projections from the ipsilateral cerebellar flocculus and ventral paraflocculus, herein referred to as the floccular lobe (Balaban et al. 1981; Dow 1937; Gerrits and Voogd 1989; Langer et al. 1985). The brain stem neurons in the rostral-medial and ventral-lateral vestibular nuclei, which receive direct projections from the floccular lobe, have been termed flocculus target neurons (Broussard and Lisberger 1992; Lisberger and Pavelko 1988; Lisberger et al. 1994a,b). The responses of these brain stem neurons largely correspond with those of a distinct physiological subclass of cells, termed eye-head (EH) neurons, which have been well characterized during eye and head movements in the head-restrained monkey (Chen-Huang and McCrea 1999; Cullen et al. 1993; Gdowski and McCrea 1999, 2000; Gdowski et al. 2001; McCrea et al. 1996; McFarland and Fuchs 1992; Roy and Cullen 2003; Scudder and Fuchs 1992; Tomlinson and Robinson 1984). In turn, EH neurons are thought to be the most significant premotor input to the extraocular motoneurons of the abducens nucleus during smooth pursuit eye movements (Cullen et al. 1993; Lisberger et al. 1994a,b; McFarland and Fuchs 1992; Scudder and Fuchs 1992). A schematic of this premotor pathway is illustrated in Fig. 3*A*.

EH neurons in the vestibular nucleus and nucleus prepositus increase their discharges in relation to eye and head movements in the same direction during smooth pursuit and cancellation of the VOR, respectively. Figure 3*B* shows an example type I EH neuron during smooth pursuit. This neuron's firing rate increased for ipsilaterally directed eye movements. Figure 3*C* illustrates the neural response of the same neuron during the VOR cancellation paradigm in which a head-restrained monkey voluntarily suppressed its VOR during passive whole-body rotation by fixating a target that moved with the head. During this paradigm, the neuron responded vigorously to ipsilaterally directed head velocity. Thus these neurons have responses similar to the gaze velocity Purkinje cells of the floccular lobe (Fukushima et al. 1999; Kahlon and Lisberger 2000; Lisberger and Fuchs 1978; Miles et al. 1980; Stone and Lisberger 1990) in that they respond similarly to changes in the direction of axis of gaze relative to space during head-restrained smooth pursuit and voluntary cancellation of the VOR.

It is important to note that in addition to playing a key role in the premotor control of smooth-pursuit eye movements, EH neurons most likely also contribute to the VOR and VCR pathways (Fig. 3*A*). First, it has been demonstrated that many EH neurons receive monosynaptic projections from the ipsilateral vestibular nerve (Broussard and Lisberger 1992; Scudder and Fuchs 1992) as well as the cerebellar flocculus. Consequently, because EH neurons send projections to extraocular motoneurons, it appears that some EH neurons together with PVP neurons constitute the intermediate leg of the direct VOR pathways. Moreover, vestibulospinal neurons that can be antidromically activated by stimulation in the cervical cord tend to fall into two categories: the non-eye-movement-related VO neurons described in the preceding text and neurons with discharge properties similar to EH neurons (Boyle 1993; McCrea et al. 1999). Thus EH neurons are likely to play a role in mediating VCR as well as other vestibulospinal reflexes.

ACTIVE HEAD MOVEMENTS. When the head is not restrained, a combination of head and eye motion (gaze pursuit) is commonly used to follow a moving visual target of interest. As during gaze shifts, an intact VOR would be counterproductive during gaze pursuit; it would generate an eye-movement signal in the direction opposite to that of the ongoing tracking. Bizzi and colleagues (Lanman et al. 1978) proposed that the eye movements generated during gaze pursuit reflect the linear summation of two opposing signals: a VOR, which cancels out the contribution of head motion to gaze, and an oculocentric pursuit signal of cerebellar origin. In support of linear summation, several subsequent studies demonstrated no difference in the frequency response of head-restrained smooth pursuit and head-unrestrained gaze pursuit (Barnes 1981; Collewijn et al. 1982; Lanman et al. 1978). However, more recent studies have shown that pursuit of faster unpredictable moving targets is improved when primates are free to move their heads (Cullen and McCrea 1990; Smith et al. 1995; Waterson and Barnes 1992).

As reviewed in the preceding text, EH neurons are thought to be the primary input to the extraocular motoneurons during ocular pursuit: they receive direct projections from the cerebellar flocculus/ventral paraflocculus, and in turn, project to the abducens motor nucleus. To date, only Roy and Cullen (2003) have specifically investigated the activity of EH neurons during gaze pursuit. In rhesus monkey, EH neuron responses during gaze pursuit were well predicted by the sum of their gaze movement sensitivity during smooth pursuit and their head-movement sensitivity during VOR. This result suggests that their responses reflect the integration of head-movement-re-



lated inputs from the vestibular afferents and gaze-movement-related information from the floccular lobe (Roy and Cullen 2003). Consistent with this proposal is the finding that the activation of neck proprioceptors via passive rotation of a monkey's body under a stationary head does not alter the EH neuron activity (Roy and Cullen 2003). It is important to note, however, that analogous experiments in squirrel monkey have suggested that EH neurons can be sensitive to neck proprioceptive inputs in this species (Gdowski and McCrea 2000; Gdowski et al. 2001).

SUMMARY. Recent studies have shown that EH neurons carry signals important for generating both head-restrained and -unrestrained gaze pursuit. Overall, the responses of EH neurons, in rhesus monkey, could be described by the sum of their gaze-velocity-related activity during smooth pursuit and their head-velocity-related activity during passive whole-body rotation in the dark. In addition, it is likely that EH neurons contribute, in part, to the VOR, VCR, and/or other vestibulospinal reflexes, however further studies are required before the role of EH neurons in mediating these reflexes will be fully understood.

FUNCTIONAL IMPLICATIONS OF DIFFERENTIAL PROCESSING OF VESTIBULAR SIGNALS

What are the implications for vestibular- and neck-related reflexes?

VOR PATHWAYS. As detailed in the preceding text, recent studies have shown that PVP neurons reliably transmit head-velocity signals when the goal is to stabilize gaze, regardless of whether the head motion is actively or passively generated. In contrast, PVP neuronal responses are attenuated whenever the behavioral goal is to redirect the visual axis of gaze relative to space. Given that PVP neurons constitute the primary interneuron of the direct VOR pathway, these results have important implications regarding the behaviorally dependent modulation of this reflex.

Over the past two decades, considerable evidence had accumulated to support the idea that the behavioral VOR is attenuated during voluntary gaze shifts. A series of experiments, in which the head was mechanically perturbed, have shown that the VOR is completely turned off during large gaze shifts (Fuller et al. 1983; Guitton and Volle 1987; Laurutis and Robinson 1986; Pélisson et al. 1988; Tomlinson and Bahra 1986) and is significantly suppressed during smaller gaze shifts (Pélisson et al. 1988; Tabak et al. 1996; Tomlinson 1990). Moreover, for gaze shifts <50°, VOR gain (defined as: change

FIG. 3. Eye-head neuron activity during passive and active head movements. *A*: the primary input to the abducens motor nuclei during smooth pursuit is thought to be from the eye-head (EH) neurons of the vestibular and prepositus hypoglossi nuclei. In addition, some EH neurons have been shown to project to the neck motoneurons and could therefore potentially play a role in mediating the VCR. *B*: EH neurons respond vigorously to eye velocity during smooth pursuit. *C*: EH neurons are activated by head velocity during voluntary cancellation of the VOR during passive whole-body rotation (VORc). The neurons prefer head motion in the same direction as eye motion during smooth pursuit. *D*: during gaze shifts, the head-velocity sensitivity of EH neurons is enhanced for both species. A model based on the neuron's head-movement sensitivity during VORd (VORd model; —) under-predicts neuronal responses. Some rhesus monkey EH neurons burst of activity during gaze shifts and most squirrel monkey EH neurons burst at the end of gaze shifts.

in eye velocity/change in head velocity caused by a perturbation) decreases as a function of increasing gaze shift amplitude (Pélisson et al. 1988; Tabak et al. 1996; Tomlinson 1990). Indeed, the responses of PVP neurons appear to provide a neural correlate for this effect; the percent attenuation of PVP head-movement-related responses during active gaze shifts increased as a function of gaze shift amplitude (Roy and Cullen 1998, 2002).

The amplitude-dependent attenuation of PVP responses during gaze shifts is consistent with known inputs from the brain stem saccadic burst generator. Burst neurons in the paramedian pontine reticular formation (PPRF) project to type II neurons in the vestibular nucleus (Sasaki and Shimazu 1981), and in turn, type II neurons send an inhibitory projection to type I (i.e., PVP) neurons (Nakao et al. 1982). Because the type II-type I vestibular projection is inhibitory, this pathway would effectively invert the "burst" behavior of burst neurons to create the "pause" in the PVP neuron responses observed during rapid redirection of gaze. The discharges of saccadic burst neurons (Cullen and Guitton 1997) and type II neurons (Roy and Cullen 2002) during gaze shifts support such a mechanism (see DISCUSSION) (Roy and Cullen 2002). Importantly, the head-velocity signals carried by saccadic burst neurons increase with gaze shift amplitude, thereby providing a greater inhibitory drive to PVP neurons during larger gaze shifts (Cullen and Guitton 1997). Moreover, in rhesus monkeys, this mechanism is consistent with the finding that the head-velocity sensitivity of PVP neurons recovers immediately after the end of a gaze shift once gaze is stable because the brain stem saccadic burst generator is inactive during this interval (Fig. 1*D*, open arrows).

It is important to note that in all investigations, to date, an average head-velocity sensitivity was estimated over an interval that spanned the entire gaze shift for each neuron. However, it is more likely that the gain of PVP neurons (and in turn VOR pathways) varies dynamically throughout this interval. The precise time course of VOR pathways attenuation during gaze shifts still remains to be determined. Most recently Tabak et al. (1996) suggested that VOR gain decreases exponentially (Tc = ~50 ms) from the onset of the gaze shift, while Huterer and Cullen (2001) concluded that the level of VOR attenuation generally decreases throughout the course of a gaze shift but that the level shows considerable variability across subjects. Thus a prediction is that the response of PVP neurons to an externally applied perturbation should become increasingly less attenuated as the gaze shift progresses.

The responses of PVP neurons are also significantly attenuated when the goal is to redirect gaze more slowly to pursue a moving target using combined eye-head gaze pursuit (Roy and Cullen 2002). A number of behavioral studies have argued for the existence of a short-latency mechanism (i.e., not mediated by smooth pursuit) that would function to modulate the gain of the VOR pathways during slow gaze redirection (Barr et al. 1976; Cullen et al. 1991; Lisberger 1990; Robinson 1982), and it is likely that the reduction in PVP modulation during gaze pursuit is a neurophysiological correlate of the observed behavioral modulation. While the attenuation of neuronal responses is less striking during gaze pursuit than during gaze shifts, it is comparable to that seen for VOR cancellation during passive whole-body rotation. These results are consistent with the proposal that differing levels of suppression during slow versus rapid gaze redirection result from the different gaze premotor circuitries that generate rapid versus slow gaze redirection. However, because less is known about the connectivity of the brain stem premotor circuits that mediate smooth pursuit and VOR cancellation than those that mediate saccades, elucidating the mechanism responsible for the attenuation in PVP neuron responses during slow gaze redirection has been less straightforward (see discussion of Roy and Cullen 2002, 2003).

In addition to PVP neurons, type II EH neurons most likely also contribute to the direct VOR pathways, even if the strength of the contribution is less than that of PVP neurons (Broussard and Lisberger 1992; Scudder and Fuchs 1992). Thus to understand the processing of vestibular signals that result from the active head movements made during gaze shifts or gaze pursuit it is important to also consider their responses. In rhesus monkey, the head-velocity sensitivities of ~50% of EH neurons during gaze shifts are enhanced relative to passive whole-body rotation in the dark (Fig. 3*D*) (Roy and Cullen 2003). A similar result has been found in squirrel monkey with the notable difference that the enhancement of head-velocity sensitivity occurred later during the postgaze shift interval (Fig. 3*D*) (McCrea and Gdowski 2003). Thus taken together these findings suggest that EH neurons may to some extent offset the reduction of PVP neuron sensitivity during and immediately after gaze shifts, in rhesus and squirrel monkeys, respectively. However, if EH neurons mediate only ~20% of direct VOR pathways in rhesus—as has been suggested by Scudder and Fuchs (1992)—then this effect would be quite modest; the summed influence of PVP and EH neurons would predict ~60% attenuation of the VOR in rhesus during large gaze shifts as compared with the 75% attenuation predicted by PVP neuron responses alone.

CERVICOOCULAR REFLEX PATHWAYS. During active head-on-body rotations, proprioceptors within the neck musculature will be strongly activated. This is not the case during passive whole-body rotations. Accordingly during active head-on-body rotations, the cervicoocular reflex (COR) could theoretically function to compliment the VOR to improve ocular stability as compared with passive whole-body rotations. Indeed, numerous studies, which have found evidence for neck proprioceptive inputs to the vestibular nuclei in decerebrate animals, are consistent with this idea (Anastasopoulos and Mergner 1982; Boyle and Pompeiano 1981; Fuller 1988; Wilson et al. 1990). However, as discussed in VESTIBULAR NUCLEI: ENCODING PASSIVE VERSUS ACTIVE HEAD MOTION, the results of more recent experiments in alert animals have provided a somewhat different view. In squirrel monkeys the majority of neurons in the vestibular nuclei that project to the extraocular motoneurons (i.e., PVP and EH neurons) are sensitive to neck motion (Gdowski and McCrea 2000). In contrast, neither static nor dynamic activation of neck proprioceptors influenced the activity of PVP or EH neurons in rhesus monkey (Roy and Cullen 2002, 2003). Similarly in cynomolgus (*M. fascicularis*) monkeys, PVP and EH neurons do not appear to be sensitive to neck inputs (Roy and Cullen 2002, 2003). The difference between the results of these studies is surprising given the same paradigms were used. However, it seems to highlight differences in the evolution of reflex strategies, in particular a difference in the importance of the COR across different spe-

cies of primates (see also discussion in McCrea and Gdowski 2003).

Prior studies have shown that COR gains are negligible to nonexistent in most species including: rhesus monkey (Bohmer and Henn 1983; Dichgans et al. 1973; Roy and Cullen 2002), human (Barlow and Freedman 1980; Bronstein 1992; Bronstein and Hood 1986; Huygen et al. 1991; Jürgens and Mergner 1989), rabbit (Barmack et al. 1981, 1989, 1992; Fuller 1980; Gresty 1976), and cat (Fuller 1980). However, squirrel monkeys appear to be an exception to this general rule; COR gains in the range of 0.4 have been reported (Godwski and McCrea 2000). It is noteworthy, that the marked difference between the COR gain of rhesus and squirrel monkeys is consistent with the apparent difference that neck proprioceptive inputs have on premotor vestibular nuclei neurons for these two species.

Thus the question remains: does the COR have any functional significance in rhesus monkeys and humans? The eye-movement response produced by the COR during head-on-body motion could, in theory, function to supplement the VOR to stabilize gaze relative to space after vestibular damage. Indeed, there is evidence for this idea in humans that the COR gain becomes more significant after bilateral loss of vestibular function and electrical stimulation of cervical afferents in patients with bilateral vestibular loss results in slow phase eye movements and catch-up saccades (Bronstein et al. 1991; Heimbrand et al. 1996; Kasai and Zee 1978; Schweigart et al. 1993). In these patients, the gain of the COR can be enhanced through training by asking subjects to change their mental set, suggesting the reflex pathway is under cognitive control (see for example, Schweigart et al. 1993). Similarly, in rhesus monkey there is evidence that after vestibular damage recovery of gaze accuracy is mediated in part by an enhancement of neck proprioceptive inputs (Dichgans et al. 1973; Newlands et al. 1999). Taken together, these results suggest that VOR pathways in rhesus monkey (i.e., PVP and/or EH neurons) might encode more significant neck related information after vestibular damage to compensate for the deficient VOR.

VCR PATHWAYS. On the one hand, the reduction of the modulation of VO neurons during self-generated head movements is consistent with their proposed role in generating the VCR. In theory, the function of the VCR is to stabilize the head in space via activation of the neck musculature, and so during voluntary head-on-body movements, the VCR would be counterproductive. Hence it might be advantageous to suppress the modulation of VO neurons during these active head movements. Moreover, prior studies in which monkeys generated active head-on-body movements while undergoing passive whole-body rotation have shown that VO neurons do not encode the active component yet continue to encode the passive component (Boyle et al. 1996; McCrea et al. 1999; Roy and Cullen 2001). This suggests that these neurons continue to generate a VCR in response to externally applied head motion as we move about in our environment. In addition to VO neurons, at least some EH neurons (Boyle et al. 1996) project directly to the cervical segments of the spinal cord. Accordingly, it seems likely that EH neurons could also contribute to the production of the VCR. However, to date, it remains to be determined whether both neuron classes project to the same muscle groups in the neck or have the same impact on muscle activation.

On the other hand, the contribution of the VCR to head stabilization is minimal in normal human subjects (Guitton et al. 1986; Peng et al. 1996). For most naturally occurring head rotations, the inertia of the head coupled with the passive viscoelastic properties of the neck plays the principal role in stabilizing the head. During yaw stabilization, its contribution is negligible when subjects are distracted by mental arithmetic (Guitton et al. 1986; Keshner and Peterson 1995). The most substantial part of active yaw axis stabilization is generated by longer-latency mechanisms, which are under voluntary control (Guitton et al. 1986). In humans, the VCR appears to be most active during pitch movements for which the head is mechanically most prone to oscillations, in the range of 1–2 Hz (Keshner and Peterson 1995; Keshner et al. 1995). Similarly, preliminary experiments suggest that the contribution of the VCR during yaw rotations is also minimal in macaque monkeys (S. G. Sadeghi and K. E. Cullen, unpublished observation). Thus it is unlikely that in macaque monkeys, or presumably humans, the principal function of the selective encoding of passive versus active head movements by VO neurons is to modulate the gain of the VCR.

The minimal reflex coupling between the vestibular system and neck is likely to allow more behavioral flexibility in the control of head movements in humans and rhesus monkeys. In contrast, Gdowski and McCrea (1999) have reported that VCR gains in squirrel monkey are on average ~0.3 at 2.3 Hz. Thus squirrel monkeys, like cats (Goldberg and Peterson 1986), presumably rely more on reflex pathways to maintain head stability. Interestingly, species differences in the behavioral relevance of the VCR are accompanied by species differences in the response properties of vestibulospinal neurons. In rhesus monkey, neck-movement responses are not typically encountered on VO or EH neurons (Roy and Cullen 2001, 2003). However, in squirrel monkey, VO and EH neurons are sensitive to horizontal neck rotation and response strength increases as a function of frequency (Gdowski and McCrea 2000). These investigators have proposed that neck proprioceptive inputs to neurons in the vestibular nuclei could be used to modify the VCR to compensate for the mechanical properties of the head and neck at higher frequencies (2.3 vs. 0.5 Hz).

If VCR gains are negligible in normal rhesus monkeys and humans, what then is the role of VO neurons in these species? There are several lines of evidence to suggest that VO neurons may be an important substrate for the perception of spatial orientation. First, prior studies have shown that VO neurons respond to low-frequency optokinetic stimulation (Boyle et al. 1985; Waespe and Henn 1977). Second, as noted in the preceding text, VO neurons are also thought to be reciprocally interconnected with cerebellar structures that are involved in vestibular processing (e.g., nodulus-uvula, flocculus, and fastigial nucleus). For example, the nodulus/uvula regions of the cerebellum are important for the coordination of gaze, head, and body posture because they are involved in transforming vestibular signals from head-fixed sensory coordinates to gravity-centered coordinates (Angelaki and Hess 1995; Wearne et al. 1998). Third, neurons in the cortex and thalamus, which receive vestibular inputs (such as areas PIVC and ventral posterior lateral thalamic nucleus, respectively), are not sensitive to eye movements (Buttner and Lang 1979; Grusser et al. 1990; Magnin and Fuchs 1977). It is most likely that these higher-order structures receive vestibular information via VO neurons because they comprise the only class of neurons in the

vestibular nucleus that are not sensitive to eye movements. Thus it is likely that selective processing of vestibular input at the level of VO neurons is most likely used by these higher-order structures to provide perceptual stability during natural behaviors.

Do the vestibular nuclei lose track of head-in-space during active gaze shifts and gaze pursuit?

As detailed in the preceding text, the VO neurons of the vestibular nuclei, receive direct inputs from vestibular afferents but do not reliably encode head velocity resulting from self-generated movements of the head on the body. Thus the primate vestibular system distinguishes between sensory inputs that arise from active self-motion of the head on the body early in processing at the level of the vestibular nuclei. This finding supports the original proposal of von Holst and Mittelstaedt (1950), who suggested that sensory inputs arising from an animal's own behavior could be distinguished from sensory inputs generated by external sources. They proposed that a copy of the motor command (i.e., a motor efference) is combined with the afferent signal to selectively remove the component caused by the motor behavior. Consistent with this proposal, an efference copy of the motor command to move the head appears to be used for the differential processing of vestibular information in monkeys, however, only in conditions where the activation of neck proprioceptors matched that expected based on the neck motor command (Roy and Cullen 2004). An analogous mechanism also has been described in the electric fish; an efference copy of the command to activate the electric organ converges centrally with electroreceptor afferent information, thereby reducing the response to self-generated electric fields (Bell 1981; Zipser and Bennett 1976).

Not only have recent experiments shown that neurons in the vestibular nuclei differentially encode passive versus active head motion (i.e., VO neurons), but they have also shown that other classes of neurons (i.e., PVP and EH neurons) differentially process head velocity during gaze redirection (e.g., gaze shifts, gaze pursuit, and VOR cancellation) versus gaze stabilization (e.g., VOR and postgaze shifts period). When taken together, these findings lead to the important question: do the vestibular nuclei completely lose track of head-in-space velocity when gaze is redirected during shifts and gaze pursuit? During gaze shifts, VO neurons continue to encode signals about passive rotations; however, they fail to reliably signal information about head velocity resulting from the voluntary head-on-body movement (Fig. 4*A*) (Boyle et al. 1996; McCrea et al. 1999; Roy and Cullen 2001). Moreover during gaze shifts, the responses of PVP neurons during both active and passive head-in-space velocity is significantly reduced (Fig. 4*B*) (McCrea and Gdowski 2003; Roy and Cullen 1998, 2002). Thus during combined eye-head gaze shifts neither neuron group reliably encodes head-in-space velocity. A similar argument can be made for the signals encoded by these neurons during gaze pursuit (not shown) (Roy and Cullen 2001, 2002). This scenario would only be further complicated by the differential sensitivity of EH neurons to head motion during gaze shifts, gaze pursuit, and immediately after gaze shifts. Thus it appears that no neuron type continues to consistently encode head-in-space velocity in the same manner under all conditions (Fig. 5, pathway A).

A

VO neuron activity during combined pWBR and active head motion

	Gaze Stabilization		Gaze Shifts	
	Rhesus monkey	Squirrel monkey	Rhesus monkey	Squirrel monkey
Passive component	No change (reliable encoding)	No change (reliable encoding)	No change (reliable encoding)	No change (reliable encoding)
Active component	↓	↓	↓	↓

B

PVP neuron activity during combined pWBR and active head motion

	Gaze Stabilization		Gaze Shifts	
	Rhesus monkey	Squirrel monkey	Rhesus monkey	Squirrel monkey
Passive component	No change (reliable encoding)	No change (reliable encoding)	↓	Data not available
Active component	No change (reliable encoding)	No change (reliable encoding)	↓	↓

FIG. 4. Summary of vestibular nuclei neuron activity during combined passive whole-body rotation and active head-on-body motion. *A*: VO neurons in both rhesus and squirrel monkey reliably encode the passive component of head-in-space motion, but responses to active head motion are significantly attenuated. Note that the observed attenuation was not dependent on the gaze monkey's gaze goal. *B*: in contrast, PVP neurons reliably encoded head-in-space velocity whenever the monkey's goal was to stabilize its gaze and not when the goal was to redirect gaze (gaze shifts). It did not matter whether the head motion was passively applied or actively generated.

What are the implications for upstream processing?

On the one hand, the arguments presented in the preceding text could lead to the conclusion that we are effectively operating as if we have a significant bilateral loss of vestibular information when we generate voluntary head movements during behaviors, such as gaze shifts and gaze pursuit. On the other hand, this seems rather unlikely because the brain has access to vestibular afferent signals via routes independent of the vestibular nuclei as well as access to inputs from other sensory modalities (e.g., proprioceptive, and optic field flow) and motor command information during natural behaviors.

Vestibular afferents project directly to cerebellar regions involved in vestibular and eye movement control, namely the nodulus/uvula, the flocculus, and the fastigial nucleus (reviewed in Voogd et al. 1996) as well as diffusely to other regions of the vestibulocerebellar vermis (Kotchabkakdi and Walberg 1978). Reliable vestibular information could thus be relayed to the cortex via cerebellar-thalamic pathways (Fig. 5, pathway B). Moreover, head-velocity information to these structures could originate from integration of signals from the vestibular nuclei and motor command (efference copy) and/or proprioceptive information. Either way, it is clear that vestibular information is encoded at these higher levels: Vestibular-related responses have been recorded in numerous cortical regions (e.g., area 7, area 3aV, parieto-insular vestibular cortex (PIVC), premotor cortex, the hippocampal formation, and fron-

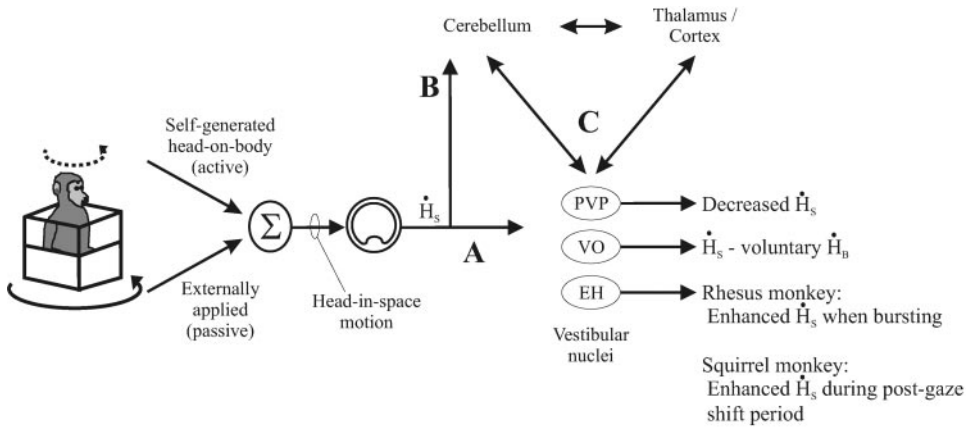


FIG. 5. Proposed mechanism for the higher-level processing of vestibular information during gaze shifts. Head-in-space velocity information, which is the sum of actively and passively generated head movements, is relayed directly to both the vestibular nuclei (pathway A) and the cerebellum (pathway B) by primary vestibular afferents. During gaze shifts, the head-velocity sensitivity of PVP neurons is markedly reduced and VO neurons only accurately encode the passive components of head-in-space. Moreover, some EH neurons have enhanced head-velocity sensitivity during or at the end of gaze shifts, in rhesus and squirrel monkey, respectively. A likely route by which intact vestibular information could reach higher centers is via the cerebellum. The cerebellum projects to the thalamus as well as to many regions of the cortex. These regions in turn project back to the cerebellum and vestibular nuclei (pathway C). $\dot{H}_S$, head-in-space velocity.

tal eye fields) that are involved in spatial representation, navigation and gaze control. In turn, many of these areas project directly back to the vestibular nuclei (reviewed in Fukushima 1997). The CNS could compute an internal estimate of self-motion via the interconnections between the vestibular nuclei, the cerebellum and cortical structures (Fig. 5, pathway C).

The vestibular projections to the hippocampus are of particular interest because this structure produces an estimate of current orientation for navigation (O'Keefe and Nadel 1979). Researchers have long speculated that the projections from vestibular nuclei (via the thalamus) contribute to the processing of spatial information in the hippocampal formation (see Smith 1997). In particular, most current models of hippocampal head direction cells compute head direction by performing an on-line integration of the animal's angular head velocity (reviewed in Sharp et al. 2001). The source of head-velocity input to these neurons during voluntary movements remains a topic of debate but is generally assumed to be the vestibular nuclei (see Brown et al. 2002). The result that vestibular information is encoded at the level of the vestibular nuclei in a behaviorally dependent manner remains to be incorporated into models of how heading direction is computed in this higher order structure. Nevertheless, it seems likely that the construction of an accurate internal representation of head direction would require the integration of multimodal (vestibular, proprioceptive, and optic field flow) sensory and motor inputs during natural behaviors.

CONCLUSIONS

Recent experiments in alert head-unrestrained monkeys have changed the way we view sensory processing in the vestibular system. While vestibular afferents similarly encode active versus passive head movements, processing at the level of the vestibular nuclei is behaviorally dependent. Single-unit recording experiments from two particular two classes of neurons in the vestibular nuclei have been particularly informative: PVP neurons, which mediate the VOR, and VO neurons, which are thought to mediate the VCR and shape vestibular information for the computation of spatial orientation by upstream structures. Neither the VOR nor VCR is a hardwired reflex, but rather both are modulated in a behaviorally dependent manner that is logically consistent with their function. The VOR functions to stabilize the visual axis in space by producing a compensatory eye movement of equal and opposite amplitude to the movement of the head. Accordingly, the head-velocity signals carried by VOR interneurons (PVP neurons) are reduced when the goal is to redirect gaze in space. The VCR functions to stabilize the head in space, via activation of the neck musculature, during head motion. Accordingly, the vestibular signals carried by VCR interneurons (VO neurons) are reduced in response to active head-on-body movements. The mechanisms that underlie this differential processing of vestibular information by PVP and VO neurons use efference copies of gaze- and neck-movement commands, respectively. It remains a challenge to understand how the differential processing of head velocity at the level of the vestibular nucleus contributes to higher-order vestibular functions such as the computation of spatial orientation and the perception of self-motion.

ACKNOWLEDGMENTS

We thank D. Watt and S. G. Sadeghi for critically reading the manuscript.

GRANTS

This study was supported by the Canadian Institutes of Health Research and Fonds de la Recherche en Santé de Québec.

REFERENCES

Abzug C, Maeda M, Peterson BW, and Wilson VJ. Cervical branching of lumbar vestibulospinal axons. *J Physiol* 243: 499–522, 1974.

Akbarian S, Grusser OJ, and Guldin WO. Corticofugal connections between the cerebral cortex and brain stem vestibular nuclei in the macaque monkey. *J Comp Neurol* 339: 421–437, 1994.

Anastasopoulos D and Mergner T. Canal-neck interaction in vestibular nuclear neurons of the cats. *Exp Brain Res* 46: 269–280, 1982.

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

Baker J, Goldberg J, and Peterson B. Spatial and temporal response properties of the vestibulocollic reflex in decerebrate cats. *J Neurophysiol* 54: 735–756, 1985.

Balaban CD, Ito M, and Watanabe E. Demonstration of zonal projections from the cerebellar flocculus to vestibular nuclei in monkeys (*Macaca fuscata). Neurosci Lett* 27: 101–105, 1981.

Barlow D and Freedman W. Cervicoocular reflex in the normal adult. *Acta Otolaryngol* 89: 487–496, 1980.

Barmack NH, Errico P, Ferraresi A, and Pettorossi VE. Interactions of cervicoocular and vestibuloocular fast-phase signals in the control of eye position in rabbits. *J Physiol* 410: 213–225, 1989.

Barmack NH, Nastos MA, and Pettorossi VE. The horizontal and vertical cervicoocular reflexes of the rabbit. *Brain Res* 224: 261–278, 1981.

Barmack NH, Pierangelo E, Ferraresi A, and Pettorossi VE. *The Head-Neck Sensory Motor System.* Oxford, UK: Oxford Univ. Press, 1992, p. 201–207.

Barnes GR. Visual-vestibular interaction in the coordination of voluntary eye and head movements. In: *Progress in Oculomotor Research*, edited by Fuchs AF and Becker W. Amsterdam: Elsevier North Holland, 1981, p. 299–308.

Barr CC, Schultheis LW, and Robinson DA. Voluntary, non-visual control of the human vestibuloocular reflex. *Acta Otolaryngol* 81: 365–75, 1976.

Bell CC. An efference copy which is modified by reafferent input. *Science* 214: 450–453, 1981.

Bilotto G, Goldberg J, Peterson BW, and Wilson VJ. Dynamic properties of vestibular reflexes in the decerebrate cat. *Exp Brain Res* 47: 343–352, 1982.

Bizzi E, Kalil RE, and Tagliasco V. Eye-head coordination in monkeys: evidence for centrally patterned organization. *Science* 173: 452–454, 1971.

Bohmer A and Henn V. Horizontal and vertical vestibuloocular and cervicoocular reflexes in the monkey during high frequency rotation. *Brain Res* 277: 241–258, 1983.

Boyle R. Activity of medial vestibulospinal tract cells during rotation and ocular movement in the alert squirrel monkey. *J Neurophysiol* 70: 2176–2180, 1993.

Boyle R, Belton T, and McCrea RA. Responses of identified vestibulospinal neurons to voluntary eye and head movements in the squirrel monkey. *Ann NY Acad Sci* 781: 244–263, 1996.

Boyle R, Buttner U, and Markert G. Vestibular nuclei activity and eye movements in the alert monkey during sinusoidal optokinetic stimulation. *Exp Brain Res* 57: 362–369, 1985.

Boyle R, Goldberg JM, and Highstein SM. Inputs from regularly and irregularly discharging vestibular nerve afferents to secondary neurons in squirrel monkey vestibular nuclei. III. Correlation with vestibulospinal and vestibuloocular output pathways. *J Neurophysiol* 68: 471–484, 1992.

Boyle R and Pompeiano O. Responses of vestibulospinal neurons to sinusoidal rotation of the neck. *J Neurophysiol* 44: 633–649, 1981.

Brandt T and Dieterich M. The vestibular cortex. Its locations, functions, and disorders. *Ann NY Acad Sci* 871: 293–312, 1999.

Bronstein AM. Plastic changes in the human cervicoocular reflex. *Ann NY Acad Sci* 656: 708–715, 1992.

Bronstein AM and Hood JD. The cervicoocular reflex in normal subjects and patients with absent vestibular function. *Brain Res* 373: 399–408, 1986.

Bronstein AM, Mossman S, and Luxon LM. The neck-eye reflex in patients with reduced vestibular and optokinetic function. *Brain* 114: 1–11, 1991.

Broussard DM and Lisberger SG. Vestibular inputs to brain stem neurons that participate in motor learning in the primate vestibuloocular reflex. *J Neurophysiol* 68: 1906–1909, 1992.

Brown JE, Yates BJ, and Taube JS. Does the vestibular system contribute to head direction cell activity in the rat? *Physiol Behav* 77: 743–748, 2002.

Buttner U and Lang W. The vestibulocortical pathway: neurophysiological and anatomical studies in the monkey. *Prog Brain Res* 50: 581–588, 1979.

Chen-Huang C and McCrea RA. Effects of viewing distance on the responses of vestibular neurons to combined angular and linear vestibular stimulation. *J Neurophysiol* 81: 2538–2557, 1999.

Chubb MC, Fuchs AF, and Scudder CA. Neuron activity in monkey vestibular nuclei during vertical vestibular stimulation and eye movements. *J Neurophysiol* 52: 724–742, 1984.

Collewijn H, Conijn P, Martins AJ, Tamminga EP, and Van Die GC. Control of gaze in man: synthesis of pursuit, optokinetic and vestibuloocular systems. In: *Physiological and Pathological Aspects of Eye Movements*, edited by Roucoux A and Crommelinck M. Hague, The Netherlands: Junk, 1982, p. 3–31.

Cullen KE, Belton T, and McCrea RA. A non-visual mechanism for voluntary cancellation of the vestibuloocular reflex. *Exp Brain Res* 83: 237–252, 1991.

Cullen KE, Chen-Huang C, and McCrea RA. Firing behavior of brain stem neurons during voluntary cancellation of the horizontal vestibuloocular reflex. II. Eye-movement related neurons. *J Neurophysiol* 70: 844–856, 1993.

Cullen KE and Guitton D. Analysis of primate IBN spike trains using system identification techniques. I. Relationship to eye movement dynamics during head-fixed saccades. *J Neurophysiol* 78: 3259–3282, 1997.

Cullen KE and McCrea RA. Gaze pursuit of predictable and unpredictable moving visual targets compared to smooth pursuit and vestibuloocular reflex cancellation. *Soc Neurosci Abstr* 16: 903, 1990.

Cullen KE and McCrea RA. Firing behavior of brain stem neurons during voluntary cancellation of the horizontal vestibuloocular reflex. I. Secondary vestibular neurons. *J Neurophysiol* 70: 828–843, 1993.

Cullen KE and Minor LB. Semicircular canal afferents similarly encode active and passive head rotation: implications for the role of vestibular efference. *J Neurosci* 22: 1–7, 2002.

Cullen KE, Roy JE, and Sylvestre PA. Signal processing by vestibular nuclei neurons is dependent on the current behavioural goal. *NY Acad Sci* 942: 345–363, 2001.

Demer JL, Oas JG, and Baloh RW. Visual-vestibular interaction in humans during active and passive, vertical head motion. *J Vestib Res* 3: 101–114, 1993.

Deutschlander A, Bense S, Stephan T, Schwaiger M, Brandt T, and Dieterich M. Sensory system interactions during simultaneous vestibular and visual stimulation in PET. *Hum Brain Map* 16: 92–103, 2002.

Dichgans J, Bizzi E, Morasso P, and Tagliasco V. Mechanisms underlying recovery of eye-head coordination following bilateral labyrinthectomy in monkeys. *Exp Brain Res* 18: 548–562, 1973.

Dow RS. Efferent connections of the flocculo-nodular lobe in *Macaca mulatta. J Comp Neurol* 68: 297–305, 1937.

Ezure K, Sasaki S, Uchino Y, and Wilson VJ. Frequency-response analysis of vestibular-induced neck reflex in cat. II. Functional significance of cervical afferents and polysynaptic descending pathways. *J Neurophysiol* 41: 459–471, 1978.

Foster CA, Demer JL, Morrow MJ, and Baloh. Deficits of gaze stability in multiple axes following unilateral vestibular lesions. *Exp Brain Res* 116: 501–509, 1997.

Fuchs AF and Kimm J. Unit activity in vestibular nucleus of the alert monkey during horizontal angular acceleration and eye movement. *J Neurophysiol* 38: 1140–1161, 1975.

Fukushima K. Corticovestibular interactions: anatomy, electrophysiology, and functional considerations. *Exp Brain Res* 117: 1–16, 1997.

Fukushima K, Fukushima J, Kaneko CRS, and Fuchs AF. Vertical purkinje cells of the monkey floccular lobe: simple-spike activity during pursuit and passive whole body rotation. *J Neurophysiol* 82: 787–803, 1999.

Fuller JH. The dynamic neck-eye reflex in mammals. *Exp Brain Res* 41: 29–35, 1980.

Fuller JH. *Control of Head Movement.* Oxford, UK: Oxford Univ. Press, 1988, p. 120–128.

Fuller JH, Maldonado H, and Schlag J. Vestibular-oculomotor interaction in cat eye-head movements. *Exp Brain Res* 271: 241–250, 1983.

Gacek RR and Lyon M. The localization of vestibular efferent neurons in the kitten with horseradish peroxidase. *Acta Otolaryngol* 77: 92–101, 1974.

Gdowski GT, Belton T, and McCrea RA. The neurophysiological substrate for the cervicoocular reflex in the squirrel monkey. *Exp Brain Res* 140: 253–264, 2001.

Gdowski GT and McCrea RA. Integration of vestibular and head movement signals in the vestibular nuclei during whole-body rotation. *J Neurophysiol* 81: 436–449, 1999.

Gdowski GT and McCrea RA. Neck proprioceptive inputs to primate vestibular nucleus neurons. *Exp Brain Res* 135: 511–526, 2000.

Gerrits NM and Voogd J. The topographical organization of climbing and fossy fiber afferents in the flocculus and the ventral paraflocculus in rabbit, cat and monkey. *Exp Brain Res* 17: 26–29, 1989.

Goldberg JM and Fernández C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. I. Resting discharge and response to constant angular accelerations. *J Neurophysiol* 34: 635–660, 1971.

Goldberg JM and Fernández C. Efferent vestibular system in the squirrel monkey: anatomical location and influence on afferent activity. *J Neurophysiol* 43: 986–1025, 1980.

Goldberg J and Peterson BW. Reflex and mechanical contributions to head stabilization in alert cats. *J Neurophysiol* 56: 857–875, 1986.

Gresty MA. A reexamination of "neck reflex" eye movements in the rabbit. *Acta Otolaryngol* 81: 3886–394, 1976.

Grossman GE, Leigh RJ, Abel LA, Lanska DJ, and Thurston SE. Frequency and velocity of rotational head perturbations during locomotion. *Exp Brain Res* 70: 470–476, 1988.

Grossman GE, Leigh RJ, Bruce EN, Huebner WP, and Lanska DJ. Performance of human vestibuloocular reflex during locomotion. *J Neurophysiol* 62: 264–271, 1989.

Grusser OJ, Pause M, and Schreiter U. Vestibular neurones in the parieto-insular cortex of monkeys (*Macaca fascicularis*): visual and neck receptor responses. *J Physiol* 430: 559–583, 1990.

Guitton D. Control of eye-head coordination during orienting gaze shifts. *Trends Neurosci* 15: 174–179, 1992.

Guitton D, Kearney RE, Wereley N, and Peterson BW. Visual, vestibular and voluntary contributions to human head stabilization. *Exp Brain Res* 64: 59–69, 1986.

Guitton D and Volle M. Gaze control in humans: eye-head coordination during orienting movements to targets within and beyond the oculomotor range. *J Neurophysiol* 58: 427–459, 1987.

Hanson JM and Goebel JA. Comparison of manual whole-body and passive and active head-on-body rotational testing with conventional rotary chair testing. *J Vestib Res* 8: 273–282, 1998.

Heimbrand S, Bronstein AM, Gresty MA, and Faldon ME. Optically induced plasticity of the cervicoocular reflex in patients with bilateral absence of vestibular function. *Exp Brain Res* 112: 372–380, 1996.

Highstein SM. The efferent control of the organs of balance and equilibrium in the toadfish, *Opsanus tau. Ann NY Acad Sci* 656: 108–123, 1992.

Hullar TE and Minor LB. High-frequency dynamics of regularly discharging canal afferents provide a linear signal for angular vestibuloocular reflexes. *J Neurophysiol* 82: 2000–2005, 1999.

Huterer M and Cullen KE. Vestibuloocular reflex dynamics during high frequency and high acceleration rotations of the head-on-body in rhesus monkey. *J Neurophysiol* 88: 13–28, 2002.

Huygen PLM, Verhagen WIM, and Nicolasen MGM. Cervicoocular reflex enhancement in labyrinthine-defective and normal subjects. *Exp Brain Res* 87: 457–464, 1991.

Jell RM, Stockwell CW, Turnipseed GT, and Geudry FE. The influence of active versus passive head oscillation, and mental set on the human vestibulo-ocular reflex. *Aviat Space Environ Med* 59: 1061–1065, 1988.

Jürgens R and Mergner T. Interaction between cervico-ocular and vestibulo-ocular reflexes in normal adults. *Exp Brain Res* 77: 381–390, 1989.

Kahlon M and Lisberger SG. Changes in the responses of Purkinje cells in the floccular coplex of monkeys after motor learning in smooth pursuit eye movements. *J Neurophysiol* 84: 2945–2960, 2000.

Kasai T and Zee DS. Eye-head coordination in labyrinthine-defective human beings. *Brain Res* 144: 123–141, 1978.

Keller EL and Daniels PD. Oculomotor related interaction of vestibular and visual stimulation in vestibular nucleus cells in alert monkey. *Exp Neurol* 46: 187–198, 1975.

Keller EL and Kamath BY. Characteristics of head rotation and eye movement-related neurons in alert monkey vestibular nucleus. *Brain Res* 100: 182–187, 1975.

Keshner EA, Cromwell RL, and Peterson BW. Mechanisms controlling human head stabilization. II. Head-neck characteristics during random rotations in the vertical plane. *J Neurophysiol* 73: 2302–2312, 1995.

Keshner EA and Peterson BW. Mechanisms controlling human head stabilization. I. Head-neck dynamics during random rotations in the horizontal plane. *J Neurophysiol* 73: 293–201, 1995.

Khalsa SB, Tomlinson RD, Schwarz DW, and Landolt JP. Vestibular nuclear neuron activity during active and passive head movement in the alert rhesus monkey. *J Neurophysiol* 57: 1484–1497, 1987.

Kotchabhakdi N and Walberg F. Primary vestibular afferent projections to the cerebellum as demonstrated by retrograde axonal transport of horseradish peroxidase. *Brain Res* 142: 142–146, 1978.

Langer T, Fuchs AF, Chubb M, Scudder CA, and Lisberger SG. Floccular efferents in the rhesus macaque as revealed by autoradiography and horseradish peroxidase. *J Comp Neurol* 235: 26–37, 1985.

Lanman J, Bizzi E, and Allum J. The coordination of eye and head movement during smooth pursuit. *Brain Res* 153: 39–53, 1978.

Laurutis VP and Robinson DA. The vestibuloocular reflex during human saccadic eye movements. *J Physiol* 373: 209–233, 1986.

Lisberger SG. Visual tracking in monkeys: evidence for short-latency suppression of the vestibuloocular reflex. *J Neurophysiol* 63: 676–688, 1990.

Lisberger SG and Fuchs AF. Role of primate flocculus during rapid behavioral modification of vestibuloocular reflex. I. Purkinje cell activity during visually guided horizontal smooth pursuit eye movement and passive head rotation. *J Neurophysiol* 41: 733–763, 1978.

Lisbereger SG and Miles FA. Role of the primate vestibular nucleus in long-term adaptive plasticity of the vestibuloocular reflex. *J Neurophysiol* 43: 1725–1745, 1980.

Lisberger SG and Pavelko TA. Brain stem neurons in modified pathways for motor learning in the primate vestibuloocular reflex. *Science* 242: 771–773, 1988.

Lisberger SG, Pavelko TA, and Broussard DM. Responses during eye movements of brain stem neurons that receive monosynaptic inhibition from the flocculus and ventral paraflocculus in monkeys. *J Neurophysiol* 72: 909–927, 1994a.

Lisberger SG, Pavelko TA, and Broussard DM. Neural basis for motor learning in the vestibuloocular reflex of primates. I. Changes in responses of brain stem neurons. *J Neurophysiol* 72 :928–953, 1994b.

Lorente De No' R. Vestibularocular reflex arc. *Arch Neurol Psychiatry* 30: 245–291, 1933.

Magnin M and Fuchs AF. Discharge properties of neurons in the monkey thalamus tested with angular acceleration, eye movement and visual stimuli. *Exp Brain Res* 28: 293–299, 1977.

McConville KMV, Tomlinson RD, and NA EQ. Behavior of eye-movement-related cells in the vestibular nuclei during combined rotational and translational stimuli. *J Neurophysiol* 76: 3136–3148, 1996.

McCrea RA and Gdowski GT. Firing behavior of squirrel monkey eye movement-related vestibular nucleus neurons during gaze saccades. *J Physiol* 546: 207–224, 2003.

McCrea RA, Chen-Huang C, Belton T, and Gdowski GT. Behavior contingent processing of vestibular sensory signals in the vestibular nuclei. *Ann NY Acad Sci* 781: 292–303, 1996.

McCrea RA, Gdowski GT, Boyle R, and Belton T. Firing behavior of vestibular neurons during active and passive head movements: vestibulospinal and other non-eye-movement related neurons. *J Neurophysiol* 82: 416–428, 1999.

McCrea RA, Strassman A, May E, and Highstein SM. Anatomical and physiological characteristics of vestibular neurons mediating the horizontal vestibuloocular reflex of the squirrel monkey. *J Comp Neurol* 264: 547–570, 1987.

McFarland JL and Fuchs AF. Discharge patterns in nucleus hypoglossi and adjacent medial vestibular nucleus during horizontal eye movement in behaving macaques. *J Neurophysiol* 68 :319–332, 1992.

Miles FA. Single unit firing patterns in the vestibular nuclei related to voluntary eye movements and passive body rotation in conscious monkeys. *Brain Res* 71: 215–224, 1974.

Miles FA, Fuller JH, Braitman DJ, and Dow BM. Long-term adaptive changes in primate vestibuloocular reflex. III. Electrophysiological observations in flocculus of normal monkey. *J Neurophysiol* 43: 1437–1476, 1980.

Minor LB and Goldberg JM. Vestibular-nerve inputs to the vestibuloocular reflex: a functional-ablation study in the squirrel monkey. *J Neurosci* 11: 1636–1648, 1991.

Minor LB, Lasker DM, Backous DD, and Hullar TE. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. I. Normal responses. *J Neurophysiol* 82: 1254–1270, 1999.

Morasso P, Bizzi E, and Dichgans J. Adjustment of saccade characteristics during head movements. *Exp Brain Res* 16: 492–500, 1973.

Nakao S, Sasaki S, Schor RH, and Shimazu H. Functional organization of premotor neurons in the cat medial vestibular nucleus related to slow and fast phases of nystagmus. *Exp Brain Res* 45: 371–385, 1982.

Newlands SD, Ling L, Phillips JO, Siebold C, Duckert L, and Fuchs AF. Short- and long-term consequences of canal plugging on gaze shifts in the rhesus monkey. I. Effects on gaze stabilization. *J Neurophysiol* 81: 2119–2130, 1999.

O'Keefe J and Nadel L. The hippocampus as a cognitive map. *Behav Brain Res* 34: 171–175, 1979.

Pélisson D, Prablanc C, and Urquizar C. Vestibuloocular reflex inhibition and gaze saccade control characteristics during eye-head orientation in humans. *J Neurophysiol* 59: 997–1013, 1988.

Peng GC, Hain TC, and Peterson BW. A dynamical model for reflex activated head movements in the horizontal plane. *Biol Cybern* 75: 309–319, 1996.

Peterson BW, Bilotto G, Goldberg J, and Wilson VJ. Dynamics of vestibuloocular, vestibulocollic, and cervicocollic reflexes. *Ann NY Acad Sci* 374: 395–402, 1981.

Peterson BW and Richmond FJ. *Control of Head Movement.* New York: Oxford Univ. Press, 1988.

Pulaski PD, Zee DS, and Robinson DA. The behavior of the vestibuloocular reflex at high velocities of head rotation. *Brain Res* 222: 159–165, 1981.

Purcell IM and Perachio AA. Peripheral patterns of terminal innervation of vestibular primary afferent neurons projecting to the vestibulocerebellum in the gerbil. *J Comp Neurol* 433: 48–61, 2001.

Robinson DA. A model of cancellation of the vestibulo-ocular reflex. In: *Functional Basis of Ocular Motility Disorders*, edited by Lennerstrand G, Zee DS, and Keller EL. Oxford, UK: Pergamon1982, p. 5–13.

Roy JE and Cullen KE. A neural correlate for vestibuloocular reflex suppression during voluntary eye-head gaze shifts. *Nat Neurosci* 1: 404–410, 1998.

Roy JE and Cullen KE. Selective processing of vestibular reafference during self-generated head motion. *J Neurosci* 21: 2131–2142, 2001.

Roy JE and Cullen KE. Vestibuloocular reflex signal modulation during voluntary and passive head movements. *J Neurophysiol* 87: 2337–2357, 2002.

Roy JE and Cullen KE. Brain stem pursuit pathways: dissociating visual, vestibular, and proprioceptive inputs during combined eye-head gaze tracking. *J Neurophysiol* 90: 271–290, 2003.

Roy JE and Cullen KE. Dissociating self-generated from passively applied head motion: neural mechanisms in the vestibular nuclei. *J Neurosci* In press.

Santina CC, Carey JP, Cremer PD, and Minor LB. Comparison of passive head impulses and sinusoidal vestibular autorotation as measures of human vestibuloocular reflex function. *Soc Neurosci Abstr* 25: 264, 1999.

Santina CC, Cremer PD, Carey JP, and Minor LB. Shortened latency and improved alignment imply preprogrammed mechanisms contribute to VOR during active head rotation after unilateral labyrinthectomy. *ARO Conference Abstr* 5233, 2000.

Santina CC, Cremer PD, Carey JP, and Minor LB. Comparison of head thrust test with head autorotation test reveals that the vestibuloocular reflex is enhanced during voluntary head movements. *Arch Otolaryngol Head Neck Surg* 128: 1044–1054, 2002.

Sasaki S and Shimazu H. Reticulovestibular organization participating in generation of horizontal fast eye movement. *Ann NY Acad of Sci* 374: 130–145, 1981.

Sato H, Ohkawa T, Uchino Y, and Wilson VJ. Excitatory connections between neurons of the central cervical nucleus and vestibular neurons in the cat. *Exp Brain Res* 115: 381–386, 1997.

Schweigart G, Heimbrand S, Mergner T, and Becker W. Interaction of vestibular and proprioceptive inputs. *J Vestib Res* 3: 41–57, 1993.

Scudder CA and Fuchs AF. Physiological and behavioural identification of vestibular nucleus neurons mediating the horizontal vestibuloocular reflex in trained rhesus monkeys. *J Neurophysiol* 68: 244–264, 1992.

Sharp PE, Tinkelman A, and Cho J. Angular velocity and head direction signals recorded from the dorsal tegmental nucleus of gudden in the rat: implications for path integration in the head direction cell circuit. *Behav Neurosci* 115: 571–588, 2001.

Shinoda Y, Ohgaki T, Futami T, and Sugiuchi Y. Vestibular projections to the spinal cord: the morphology of single vestibulospinal neurons. *Prog Brain Res* 76: 17–27, 1988.

Smith PF. Vestibular-hippocampal interactions. *Hippocampus* 7: 465–471, 1997.

Smith WAD, Segal B, and Cullen KE. Eye and head coordination during head-free gaze pursuit in the rhesus monkey: predictable vs. unpredictable stimuli *Soc Neurosci Abstr* 21, 1995.

Stone LS and Lisberger SG. Visual responses of Purkinje cells in the cerebellar flocculus during smooth-pursuit eye movements in monkeys. I. Simple spikes. *J Neurophysiol* 63: 1241–1261, 1990.

Tabak S, Smeets JBJ, and Collewijn H. Modulation of the human vestibuloocular reflex during saccades: probing by high-frequency oscillation and torque pulses of the head. *J Neurophysiol* 76: 3249–3263, 1996.

Thurtell MJ, Black RA, Hlmagyi GM, Curthoys IS, and Aw ST. Vertical eye position-dependence of the human vestibuloocular reflex during passive and active yaw head rotations. *J Neurophysiol* 81: 2415–2428, 1999.

Tomlinson RD. Combined eye-head gaze shifts in the primate. III. Contributions to the accuracy of gaze saccades. *J Neurophysiol* 64: 1873–1891, 1990.

Tomlinson RD and Bahra PS. Combined eye-head gaze shifts in the primate. II. Interactions between saccades and the vestibuloocular reflex. *J Neurophysiol* 56: 1558–1570, 1986.

Tomlinson RD and Robinson DA. Signals in vestibular nucleus mediating vertical eye movements in monkey. *J Neurophysiol* 51: 1121–1136, 1984.

Voogd J, Gerrits M, and Ruigrok JH. Organization of the vestibulocerebellum. *Ann NY Acad Sci* 781: 553–579, 1996.

von Holst E and Mittelstaedt H. Das reafferenzprinzip. *Naturwissenschaften* 37: 464–476, 1950.

Waespe W and Henn V. Neuronal activity in the vestibular nuclei of the alert monkey during vestibular and optokinetic stimulation. *Exp Brain Res* 27: 523–538, 1977.

Waterston JA and Barnes GR. Visual-vestibular interaction during head-free pursuit of pseudorandom target motion in man. *J Vestib Res* 2: 71–88, 1992.

Wearne S, Raphan T, and Cohen B. Control of spatial orientation of the angular vestibuloocular reflex by the nodulus and uvula. *J Neurophysiol* 79: 2690–2715, 1998.

Wheatley BP. Feeding and ranging of east Bornean *Macaca fascicularis.* In: *The Macaques: Studies in Ecology, Behavior and Evolution.* edited by Lindburg DG. Princeton, NJ: Van Nostrand, 1980, p. 215–246.

Wilson VJ, Yamagata Y, Yates BJ, Schor RH, and Nonaka S. Response of vestibular neurons to head rotations in vertical planes. III. Response of vestibulocollic neurons to vestibular and neck stimulation. *J Neurophysiol* 64: 1695–1703, 1990.

Zipser B and Bennett MV. Interaction of electrosensory and electromotor signals in lateral line lobe of a mormyrid fish. *J Neurophysiol* 39: 713–721, 1976.

J Neurophysiol 93: 1820–1821, 2005.
doi:10.1152/jn.01078.2004.

Volume 91, April 2004

Pages 1883–1898: Hurtado JM, Rubchinsky LL, and Sigvardt KA. "Statistical Method for Detection of Phase-Locking Episodes in Neural Oscillations" (doi:10.1152/jn.00853.2003; http://jn.physiology.org/cgi/content/full/91/4/1883). There is an error in *Equation 7* (p. 1887). The correct equation is shown here:

$$\mathrm{SNR}(t) = \frac{\max\limits_{\omega_a \le \omega \le \omega_b} \{P(\omega,t)\}}{\operatorname{avg}\limits_{\omega_0 \le \omega \le \omega_{max}} \{P(\omega,t)\}}$$

where

$$\max_{\omega_a \le \omega \le \omega_b} \{P(\omega,t)\}$$

is the maximum value of $P(\omega,t)$ in the oscillatory band $[\omega_a,\omega_b]$ and

$$\operatorname{avg}_{\omega_0 \le \omega \le \omega_{max}} \{P(\omega,t)\}$$

is the average value in the broader band $[\omega_0, \omega_{max}]$.

The correct expression gives the ratio of peak to average power, and it can take any value >0. This is the signal-to-noise ratio (SNR) that the authors implemented in the computational routines. The original (incorrect) expression is the ratio of (total) power in the oscillatory band over total power, and it cannot take values above 1. This (previous) definition does not make sense, given that the authors are using the criterion SNR > 3.7. In a preliminary analysis, the first formula was used, but latter it was decided that the second one was more appropriate; however, the wrong formula was retained in the final version of the accepted manuscript.

Volume 91, May 2004

Pages 1919–1933: Cullen KE and Roy JE. "Signal Processing in the Vestibular System During Active Versus Passive Head Movements" (doi:10.1152/jn.00988.2003; http://jn.physiology.org/cgi/content/full/91/5/1919). Previous to the summary of the section titled "VESTIBULAR NUCLEI: ENCODING PASSIVE VERSUS ACTIVE HEAD MOTION," a paragraph (on page 1923 of the printed article) misrepresented the name of Dr. C. C. Della Santina, who should be cited as "Della Santina" rather than simply "Santina." This error is also present in the bibliography, which cited 3 articles by Dr. Della Santina and colleagues. The corrected text is below, followed by the proper citations.

"Results in rhesus monkey are consistent with accumulating evidence in human that VOR gains are generally comparable during passive and active rotations of the head-on-body (Della Santina et al. 1999, 2000, 2002; Foster et al. 1997; Hanson and Goebel 1998; Pulaski et al. 1981; Thurtell et al. 1999) as well as the finding that neither neck proprioceptors nor motor efference copy inputs alter VOR response dynamics in this primate species (Huterer and Cullen 2002). Results in squirrel monkey suggest that in this species VOR gain should be sensitive to reafferent sensory and motor inputs during active movements."

Della Santina CC, Carey JP, Cremer PD, and Minor LB. Comparison of passive head impulses and sinusoidal vestibular autorotation as measures of human vestibuloocular reflex function. *Soc Neurosci Abstr* 25: 264, 1999.

Della Santina CC, Cremer PD, Carey JP, and Minor LB. Shortened latency and improved alignment imply preprogrammed mechanisms contribute to VOR during active head rotation after unilateral labyrinthectomy. *ARO Conference Abstr* 5233, 2000.

Della Santina CC, Cremer PD, Carey JP, and Minor LB. Comparison of head thrust test with head autorotation test reveals that the vestibuloocular reflex is enhanced during voluntary head movements. *Arch Otolaryngol Head Neck Surg* 128: 1044–1054, 2002.

Volume 92, September 2004

Pages 1928–1936: Richter TA, Dvoryanchikov GA, Chaudhari N, and Roper SD. "Acid-Sensitive Two-Pore Domain Potassium (K_2P) Channels in Mouse Taste Buds" (doi:10.1152/jn.00273.2004; http://jn.physiology.org/cgi/content/full/92/3/1928). Although Table 1 appears in complete form in the first-published version of this article (Article in PresS, http://jn.physiology.org/cgi/reprint/00273.2004v1), during production of final version of this article, two lines of text were lost from Table 1, which should have listed information (primer sequences, GenBank accession numbers, and other items) for K channels TREK-2 and TRESK. The complete, corrected Table 1 is listed here (with the original legend).

TABLE 1. *RT-PCR primer sequences and GenBank accession numbers for each of the eight K_2P channels examined in the present study.*

K Channels	Other names	Gene	Accession Number	Forward Primer	Reverse Primer	Product size (bp)
TWIK-1, K_{2P} 1.1	hOHO	KCNK1	NM_008430	5′-ccgagagctgtacaagatcg-′3	5′-tgcccagggattaaaacc-′3	442
TREK-1, K_{2P}2.1	TPKC1	KCNK2	U73488	5′-tggaaacatctccccacg-′3	5′-ccaatcatcatgctcagaacagc-′3	442
TASK-1, K_2P3.1	TBAK-1, OAT-1	KCNK3	AF065162	5′-cgcctcaagccgcacaag-′3	5′-acacgaaaccgatgagcacca-′3	295
TASK-2, K_2P5.1		KCNK5	BC058164	5′-atggtgacagaagaatgga-′3	5′-tgagatacctcttccaagc-′3	539
TWIK-2, K_2P6.1	TOSS	KCNK6	AF110521	5′-tgttcactgccagcatcc-′3	5′-gctctgagaaggtctctactgc-′3	486
TASK-3, K_2P9.1		KCNK9	AF391084*	5′-agctggagctggtaatcctg-′3	5′-cggtcaccatgttctccata-′3	303
TREK-2 K_{2P}10.1		KCNK10	NM_023096*	5′-accctgttcctcgactctcc-′3	5′-agattttgcctccttcagtgc-′3	435
TRESK			XM_285304	5′-ttcttctgctgcacagtgttc-3′	5′-aatctctcaaacagctccacat-3′	375

*Unless otherwise specified, accession numbers are for mouse sequence.

Volume 92, October 2004

Pages 2555–2573: Lee AK and Wilson MA. "A Combinatorial Method for Analyzing Sequential Firing Patterns Involving an Arbitrary Number of Neurons Based on Relative Time Order" (doi:10.1152/jn.01030.2003; http://jn.physiology.org/cgi/content/full/92/4/2555). This article cited an earlier publication by Lee and Wilson (Lee AK and Wilson MA. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36: 1183–1194, 2002). This citation was incorrectly listed in the bibliography with a publication year of 2000. This error also occurs throughout the text of the article, wherever this citation is mentioned. The correct year should be 2002.

Volume 92, November 2004

Pages 3142–3147: Sasaki S, Isa T, Pettersson LG, Alstermark B, Naito K, Yoshimura K, Seki K, and Ohki Y. "Dexterous Finger Movements in Primate Without Monosynaptic Corticomotoneuronal Excitation" (doi:10.1152/jn.00342.2004; http://jn.physiology.org/cgi/content/full/92/5/3142). In the final-published version of this article, the acceptance date for this article was listed with the wrong year (just below the affiliation line on the first page). This article was accepted on May 25, 2004, after submission on April 2, 2004.