Abstracts: Vestibular Influences on Movement Satellite Meeting

SP1.1

Afferent responses to mechanical stimulation and drug application in mouse in-vitro labyrinth

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In a recently developed in vitro preparation of the mouse labyrinth we have recorded intra-axonally from anterior and horizontal primary afferents, close to the base of their respective cristae (<500 microns from hair cell/afferent synapse). We have mapped the position and background discharge rates of afferents to both cristae. Despite the trauma associated with isolation from the skull and lower recording temperatures (23 to 34 degrees C), bony labyrinths retain their ability to transduce mechanical stimulation into afferent discharge. Using a micropusher to indent exposed windows of membranous labyrinth we have characterised the response properties of both anterior and horizontal canal afferents. We studied afferent activity in response to sinusoidal indentations of the corresponding membranous canal and compared these results with those obtained by stimulating the adjacent canal.

In recordings from 97 afferents over a range of frequencies from 0. 01 to 10 Hz, afferents responded with sinusoidal changes in discharge rates and modulation of membrane potential in a predictable manner. Phase response of afferent discharge was characterised by frequency-dependent shifts in peak activity. Peak activity was always in advance of maximum indentation, with large phase leads at low frequencies (106 ± 28. 1 degrees for 0. 01 Hz; mean ± s. d.). The smallest phase leads occurred around 1 Hz; 15 ± 29. 3 degrees. These phase shifts are similar to those reported in in vivo recordings from mammals, despite our use of artificial rather than natural stimuli. Calculation of gain was more problematic, probably because indentation partially collapsed the canal. This made it difficult to provide consistent stimuli. Consequently while gain could be calculated for individual units these results could not be pooled across animals. This in vitro preparation also allows application of drugs and we have begun to study the effects of various neuromodulators on afferent discharge.

Our preliminary results suggest that TTX (1 uM) abolishes afferent discharge by acting directly on axons because its effect occurs within 30 seconds or less. CNQX (10 uM) can take up to 6 minutes to abolish background afferent activity suggesting that it probably acts at the hair cell / primary afferent synapse. Afferent activity was abolished much faster (< 60 seconds) after initial application and washout (10 mins) of CNQX, suggesting that the drug remains bound to receptors for some time. In conclusion, despite the drawbacks associated with gain calculations, isolated mouse in vitro labyrinths are viable preparations for studying transduction and synaptic mechanisms in the mammalian peripheral vestibular apparatus.

SP1.2

Presynaptic Ca channels in frog semicircular canal hair cells

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L-type calcium channels have been shown to be the major contributor to calcium currents in vestibular hair cells; however, increasing evidence suggests that non-L components are also involved. As calcium currents vary across the epithelium along presumed physiological gradients, the relative contribution and importance of these different calcium channels, particularly the non-L components, might subserve distinct presynaptic functions.

In the present work, we performed both Western blot and immunocytochemical experiments to test for the expression of the various calcium channel alpha1 subunits. In agreement with previous mRNA results and observations made in the frog saccule, hair cells from the frog semicircular canal (SCC) were marked by antibodies for alpha1D and alpha 1B. Immunostaining was punctate, suggesting the presence of channel clusters. In addition, the clusters themselves were not homogeneously distributed within the cell, but typically found in groups which corresponded in number and size to the Ca hotspots previously observed in these hair cells.

In whole-cell patch clamp experiments performed in the perforated patch configuration, the application of the L-type blocker nimodipine and the N-type blocker w-conotoxin GVIA on SCC hair cells was sometimes, although not always, able to completely block barium currents. P/Q-type blockers were always ineffective. This suggests that the non-L component may also include R-type channels, at least in some cells. Since the selectivity of the available alpha1E antibodies for frog channels is unclear we tested the recently available R-type calcium channel blocker, SNX-482, alone and in combination with nimodipine and w-conotoxin GVIA, to test for the functional pre-

sence of alpha1E. In addition, the involvement of each component in afferent transmitter release was tested by monitoring the effects of these three Ca channel blockers on membrane capacitance increases evoked by cell depolarization.

P1.3

Voltage responses of type I and type II hair cells of the chick embryo semicircular canal

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We recently found that in the chick embryo semicircular canal both type I and type II hair cells differentiate along with embryonic development; at hatching both hair cell types express mature-like morphological and electrophysiological features, also in relation to their location in the sensory epithelium. Type I hair cells were identified by their typical amphora shape, and by the presence of IK,L, their signature current, which is responsible for their low-gain voltage response to stimulus currents.

In addition to IK,L the expression of other ion channels distinguishes the voltage responses of type I and type II hair cells, and of type II hair cells located in different zones of the sensory crista. The role of these channels in shaping hair cell voltage response has been further investigated here by using a variety of voltage- and current-clamp protocols.

Our results show that the size of the depolarization produced by a positive current step depends on the membrane voltage (Vm) before the step, in a way that is distinctive for different hair cells subpopulations. In type II hair cells expressing the transient outward rectifying K current IKA the depolarization produced by the test step is reduced by hyperpolarizing Vm; on the contrary, in type II hair cells expressing the slow inward rectifying current Ih the depolarization is transiently increased by hyperpolarizing Vm. In cells expressing both currents, IKA dominates the response; in cells lacking both currents the size of depolarization is not affected by previous hyperpolarizations. In type I hair cells, the response is similar as in type II hair cells expressing Ih, i. e. a transient increase of the depolarization upon hyperpolarization conditioning. The extent of this effect depends on the relative quantity of IK,L active at the resting (or imposed) membrane potential.

The above findings suggest that different classes of hair cells will process the same excitatory stimulus in a different way also depending on their previous potential.

SP1.4

Junctional transmission in calyx-bearing and bouton afferents in the turtle posterior crista

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Intracellular recordings are made from afferent fibers near the crista. Activity is modulated by sinusoidal indentation of the canal duct. To study synaptic traffic in isola-

tion, spikes are blocked with TTX. Under these conditions, both quantal and nonquantal transmission is observed. Quantal transmission is indicated by the presence of discrete potentials of 0. 1-0. 8 mV, which peak in 1-3 ms and then decline in 5-15 ms. The potentials have the properties of mEPSPs: they are TTX-insensitive, are blocked in low Ca high Mg solutions, and are randomly timed. mEPSPs are abolished by CNQX, but are unaffected by AP-5, suggesting that transmission involves non-NMDA glutamate receptors. Shifts in membrane potential during sinusoidal stimulation are larger than can be ascribed to modulation of quantal rate, implying the presence of nonquantal transmission. The implication is confirmed by the observation that potential shifts persist after quantal transmission is blocked.

In the present study, we have been able to distinguish calyx-bearing (CD) afferents from bouton (B) afferents by their characteristic responses to electrical activation of efferent fibers. The two kinds of fibers differ in both their quantal and nonquantal transmission. mEPSPs are smaller and briefer in CD units. Quantal rates are similar in the two fiber classes with background rates of 500-2000 /s. Excitatory identations typically double the rate, while inhibitory identations can silence quantal activity. Stimulation results in a peak-to-peak potential shift of 3 - 4 mV. On average, the nonquantal component makes up 60% of the total shift in CD units as compared to 20% in B units. The mechanisms of nonquantal shifts has yet to be determined. But as it is the membrane shift which results in the modulation of afferent discharge, the nonquantal component would appear to be of functional importance especially in CD units. (Supported by NIH DC 02058-06)

SP1.5

Responses of irregular vestibular nerve afferents to high-frequency rotations

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Regularly discharging vestibular nerve afferents innervating the semicircular canals have been shown to respond linearly even at very high frequencies. Nonlinear responses of irregularly discharging afferents such as inhibitory cutoff have been qualitatively documented in the past. A quantitative description of the linear and nonlinear responses of irregularly firing afferents to high-frequency sinusoidal stimulation were investigated here.

Recordings in chinchillas from 107 afferents with a normalized coefficient of variation of $> 0. 1$ form the basis of this report. Linear responses were maintained for 17 high-gain (0.35 CV* $\pm$ 0. 1) and 15 low-gain (0. 7 CV* $\pm$ 0. 29) afferents over a frequency range of at least 2-8 Hz. The total frequency range tested extended from 0. 5-20 Hz. Nonlinear responses were obtained in 50 afferents over a frequency range of 2-20 Hz.

At 2 Hz, high-gain afferents had a sensitivity (mean $\pm$ sd) of 1. 4 $\pm$ 0. 7 spikes/sec per deg/sec and a phase lead of 26. 9 $\pm$ 10. 5 deg re velocity. At 12 Hz, high-gain afferents had a sensitivity of 2. 7 $\pm$ 1. 6 and a phase lead of 56. 8 $\pm$ 15. 3. A simple transfer function of the form (tv s + 1) fits

the data well. The time constant tv is equal to 0. 0082[log(G) + 0. 0165], where G = the gain of the afferent at 2 Hz. This transfer function has a lower phase lead than found in the data in the range 2-6 Hz, however. A closer approximation may be gained using the transfer function (tv s + 1)k, where tv = 0. 2G - 0. 26 and k = -0. 07G + 0. 81.

At 2 Hz, low-gain afferents had a sensitivity of 0. 57 $\pm$ 0. 27 and a phase lead of 35. 5 $\pm$ 8. 7. At 12 Hz, low-gain afferents had a sensitivity of 1. 72 $\pm$0. 82 and a phase lead of 70. 6 $\pm$ 18. 0. These findings indicate that, at higher frequencies, the difference in sensitivity between high and low-gain afferents becomes less apparent.

Nonlinear responses of afferents were predominantly due to rectification and synchronization of responses. An absolute cutoff for rectification was not noted. Synchronization of responses tended to occur above a rotational acceleration of 1000 deg/s^2. Afferents tended to emerge from inhibitory cutoff (begin firing) leading velocity by 90 degrees. The velocity window over which they began firing remained stable at various frequencies and velocities, indicating a linear signal to the spike generator. (Supported by NIH R01 DC02390)

SP1.6
Responses to low and high intensity stimuli in chinchilla semicircular canal afferents
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It is usually assumed that mammalian afferents do not have a threshold and that their responses are linearly related to rotation intensity. We studied both issues. To study thresholds, we recorded from horizontal- and superior-canal afferents Averaged responses to several 2-s excitatory velocity ramps (Vmax=10 deg/s) were fit in each of 30 units by the step response of a first-order torsion pendulum with a threshold term. Computed thresholds were not statistically different from zero. Based on a fit to the response averaged over the 30 units, any threshold would be <1 deg/s. Results were similar in regular and irregular units. There was no evidence for a threshold also in the inhibitory direction.

To define the linear range of the response and to determine its relation to the discharge regularity and the presumed morphological class of the unit. Excitatory response-intensity functions were derived from the discharge 1. 5 – 2. 0 s after the start of velocity ramps (range: 10-875 deg/s) and were fit by a function, $r(V) = r_{MAX}[V/(V_{1/2} +V)]$, relating response $r(V)$ to angular velocity V, with r_{MAX} as the maximal response and $V_{1/2}$ the velocity producing half-maximal responses. Among non-calyx units, linear (near-zero) gains (G) ranged from 0. 1 to 1. 2 spikes•s^{-1}/deg•s^{-1} and had strong inverse linear correlation to discharge regularity. For calyx units G averaged ($\pm$ SEM) 0. 34 $\pm$ 0. 03 spikes•s^{-1}/deg•s^{-1}. $V_{1/2}$ is a measure of the linear range. For regular (CV*<0. 05; n=20), intermediate (0. 05<CV*<0. 2; n=11), and dimorphic irregular (CV*>0. 2, n=4), units the mean values of $V_{1/2}$ are 2200 $\pm$ 300, 700 $\pm$ 100 and 400 $\pm$

50 deg/s, respectively. For calyx units (n=12), $V_{1/} = 1800 \pm 400$ deg/s.

We calculated the predicted response values for 560 deg/s based on the extrapolaion of the values of G. For regular, intermediate, irregular dimorphic and calyx units the actual response was on average smaller then the predicted response by 20, 46, 62 and 26 percent, respectively. The mean value of r_{MAX} for all units was 480 $\pm$ 40 spikes/s and was not significantly different between unit classes. The maximal discharge (r_{MAX} + resting discharge), was estimated to be 530 $\pm$ 30 spikes/s.

In summary, afferent responses maintain linearity in the physiological range of intensities. There are no thresholds. Regular units, and calyx units extend the range over which the response is linear. (Supported by NIH RO1 DC 03946)

SP1.7
Intra-axonal recordings from canal afferents in the mouse in-vitro labyrinth
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We have studied canal afferent responses to sinusoidal indentation of the membranous canal in an in vitro preparation of the mouse labyrinth, using a micropusher. When recording at the base of the crista (less than 500 microns) from the hair cell synapse we have observed not only modulation of canal afferent discharge activity, but a modulation (up to 5 mV) of membrane potential, (Vm) in the majority of afferents. In this preparation we were able to access both anterior and horizontal afferents and therefore compare the response properties from these two groups of canal afferents when stimulating a single canal. During anterior canal stimulation (canal-side of the ampulla) we observed increased discharge activity in response to withdrawal of the micropusher, while activity in the horizontal canal afferents decreased. Similarly, anterior and horizontal afferent Vm modulations were also opposed. Unlike afferent discharge, however, the phase of peak Vm was not dependent on stimulation frequency, instead Vm modulation remained in phase (or out of phase) with the stimulus profile. The opposing effect on anterior and horizontal canal afferent discharge in response to anterior canal indentation may be explained by the opposite polarisation of hair cells within the two ampullae.

To test whether Vm modulations may be due, in part, to an electrical rather than a mechanical effect we assessed the response to small current steps injected into the impaled afferent axon during 1 Hz sinusoidal stimuli. Vm modulation could be nullified by injections of positive current (approx. 200 pA) and phase-inverted by still larger positive currents (300 - 500 pA). In contrast, although afferent discharge rate predictably increased during current injections, the phase of peak discharge activity to sinusoidal stimulation remained unchanged. To determine if Vm modulation was related to hair cell activity we bath-applied the mechanotransducer channel blocker, streptomycin sulfate

(1 mM). Afferent discharge was reversibly blocked by streptomycin application within 60 seconds but Vm was unaltered even after 10 minutes of exposure. Due to the speed of block and its reversibility we believe that streptomycin applied on the perilymphatic side had a direct effect on the afferent nerve and may not have penetrated the endolymphatic space in sufficient concentration to act upon the hair cell mechanotransducer channels. In another experiment simply opening the membranous labyrinth, prior to streptomycin application, appeared to abolish Vm.

We hyothesise that piezoelectric-like variations in endolymphatic potential may provide the source of Vm modulation in afferent axons. (Supported by National Health and Medical Research Council of Australia, Garnett Passe and Rodney Williams Foundation, Hunter Medical Research Institute to AMB and RJC.)

SP1.8
A cellular and pharmacological analysis of efferent responses in turtle posterior crista afferents
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In the turtle posterior crista, there is heterogeneity in the responses of afferents to electrical stimulation of efferent fibers. Many bouton afferents (BT/BM) are inhibited whereas calyx-bearing afferents (CD) are excited. Intracellular recordings were made from these afferents close to the posterior crista to record synaptic potentials during and after efferent activation. Our results show that efferent-mediated inhibition in bouton afferents most likely results from the presynaptic (i. e. efferent to hair cell) activation of alpha9/alpha10-containing nicotinic receptors (a9/10nAChRs) functionally coupled to the activation of small-conductance, calcium-dependent potassium channels (SK). Consistent with this suggestion, the inhibition is 1) associated with a reduction in the frequency of mEPSPs; 2) completely antagonized by cholinergic antagonists known to block a9/10-nAChRs, and; 3) converted into an excitatory response following treatment with selective SK blockers. During SK blockade, efferent stimulation produces a large depolarizing postsynaptic potential (PSP) that is also completely blocked by a9/10nAChR antagonists. A portion of the efferent-mediated depolarization may be postsynaptic (i. e. efferent to afferent) because the PSP is not completely abolished by glutamate-receptor antagonists that appear to eliminate quantal transmission from hair cells. Since the remaining efferent-mediated depolarization is also completely antagonized by a9/10-nAChRs blockers, the same nicotinic receptors may underlie both the presynaptic and presumed postsynaptic components. Efferent-mediated excitation of calyx afferents is characterized by a large postsynaptic depolarization without an appreciable change in mEPSP frequency. The pharmacology of efferent excitation remains to be worked out.

By iontophoresing the charged lidocaine deriviative, QX-314, from the recording microelectrode into the afferent, we can successfully abolish afferent action potentials while continuing to stimulate efferent pathways. A number of interesting observations have been made using this technique. Both BM/BT and CD afferents respond to single shocks which speaks to the power of the efferent system. In BM/BT afferents, the voltage response to a single efferent shock consist of a brief depolarization (~10 ms) followed by a pronounced hyperpolarization (~350 ms). Both components are blocked by a9nAChR antagonists and the depolarization can be enhanced and isolated using SK blockers. CD units also respond to single shocks of efferent fibers. The kinetics of these single shock responses suggest at least two excitatory components. However, the neurochemical and biophysical basis for this response has not been resolved. (Supported by NIH DC 02058-06 and T-32DC 00058-01).

SP1.9
A report of 2 cases of ageotrophic horizontal canal benign paroxysmal positional vertigo managed with a new head shaking method and analyses of the results of 25 cases
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Background and Objectives : Ageotrophic nystagmus in horizontal canal BPPV has been explained by cupulolithiasis theory, and has been reported to have a less therapeutic response to conservative rehabilitation than the other type of BPPV. Though methods to detach the debris with a vibrator or modified Semont maneuver have been introduced, the low frequency vibrator itself is not physiologic and the effectiveness of these methods have been questioned. Therefore we would like to introduce a new strategy using head shaking as a more convenient, physiologic method. Materials and Method : 25 cases of ageotrophic nystagmus at roll test were selected (male to female ratio was nine to 16; mean age was 54; age distribution was 25 to 75) retrospectively. Seven cases were excluded because of compound BPPV, bilateral BPPV and secondary serial BPPV. Remain 18 cases was divided by two groups (a head shaking group (nine cases), non-head shaking group (nine cases)), and then number of clinic visits for treatment was compared between both groups. Criteria of treatment success were the disappearance of all nystgmus at repeated roll test or improvement of vertigo disability index (less than 2) at the end of treatment. Head shaking was done about the yaw axis, over 120 degrees, 10-20 times. If ageotrophic nystagmus disappear after head shaking, it was sufficient to just maintain head position for several hours; if it converted to the geotrophic form, convenional barbecue rotation was performed to the healthy side; if no change of nystagmus could be seen, the above protocol was repeated. Result: The number of visits was 1.1 times in head shaking group, but it was 1.9 times in non- head shaking. 6 cases converted to the geotrophic form in both groups. Conclusion: A new strategy using head shaking may have some benefit as like a way to understand the patho-physiologic mechanism while maintaining high therapeutic efficacy with a simple and easy procedure.

SP1.10

Properties of adaptation in hair cells of the mouse utricle

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Mammalian utricular hair cells detect low-frequency head movements and steady head position. In the semi-intact preparation of the mouse utricle (postnatal days 0-10), we investigated whether adaptation is slowed or reduced to enhance performance at low frequencies. Whole-cell transduction currents were recorded in response to step displacements of the bundle effected with a coupled, stiff glass probe with a rise time of ~1 ms. There were no systematic differences with hair cell location (striolar or extrastriolar) or type (I or II) in the time course and extent of adaptation or in other aspects of transduction: operating range, resting open probability and maximum current. Thus, under these conditions transduction properties are homogeneous. At half-maximal activation, adaptation was well fit by a single exponential function: average time constant 30 ± 2 ms and average 76 ± 3 % decay at steady state. Transducer adaptation could contribute to high-pass filtering of some vestibular afferent responses to low frequency head movements (<2 H).

To look for a faster component of adaptation we deflected mouse and frog hair bundles with a stiff probe with a ~200 us rise time. For the mouse data, monoexponential fits produced a mean time constant of 18 ± 3 ms (n=44) significantly faster than for the slower probe. Moreover, for most data, the decay was better fit with a double exponential function with mean fast and slow time constants of 5 ± 1 ms and 45 ± 4 ms. For five frog saccular hair cells, mean time constants were 2 ± 1 ms and 18 ± 4 ms. In both mouse and frog cells, the amplitude of the slow component rose with stimulus size. The fast component has been put forth as an amplifying mechanism that tunes hair cells to particular frequencies. The time constant that we observed would tune mouse hair cells at frequencies well above the presumptive natural stimulus frequency range of mammalian vestibular organs.

Adaptation shifts the instantaneous current-displacement (I(X)) relation along the displacement axis in the direction of the step. In frog saccular hair cells, the total shift is a constant percentage of the adapting step, and as a result the steady-state I(X) relation is a stretched version of the instantaneous relation (Shepherd and Corey 1994). However, in some mouse utricular hair cells, the shift as a percentage of the adapting step increased for large displacements, producing compression of the steady-state I(X) relation. This difference relative to frog cells allows the mouse cells to report novel stimuli over a larger range of background stimuli.

SP1.11

Directional selectivity and dynamic responses of vestibular afferents following regeneration from ototoxic damage

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The vestibular system provides for compensatory reflexive behaviors such as postural adjustments and oculomotor responses that occur as the head rotates or when the body shifts relative to gravity. Aminoglycoside antibiotics are known to produce hair cell death and afferent damage, both of which regenerate over time. The primary objective of the present study was to determine the functional capacity of the regenerated vestibular afferents in birds that have undergone treatment with streptomycin. Neural recordings from semicircular canal afferents were obtained during rotational motion, in both normal and birds undergoing regeneration from 4 days to 1 year post-treatment. Each afferent was characterized as a posterior, horizontal or anterior canal fiber using rotations in different planes. Once identified, the responses to sinusoidal stimuli at frequencies ranging $0.02 - 4.0$ Hz were obtained. The head orientation relative to the rotation axis was systematically changed and direction of maximum sensitivity vector for each canal afferent was determined. To date, responses from canal afferents (N=21) show that following 9 months to 1 year of post-treatment regeneration, the mean gains at mid range frequencies (0.5 - 2 Hz) of regenerated horizontal and vertical canal afferents are not significantly different from normal values. Response phases of regenerated afferents had also returned to normal values. The transfer functions for responses to rotations between 0.02 and 4 Hz will be presented, along with the maximum sensitivity directions. Anatomical reconstructions of regenerated afferents following 9 months to one year post-treatment survival, show that the three main types of afferents return, including calyx, dimorph, and bouton fibers. However, the innervation patterns of fully regenerated fibers are different than normal afferents, with smaller terminal fields, smaller calyces, and fewer boutons.

SP1.12

Vestibular neuritis visualized by 3 Tesla MRI

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Background. Vestibular neuritis is a sudden idiopathic unilateral loss of vestibular function, usually affecting the function of the organs innervated by the superior vestibular nerve. It has been suggested that reactivation of herpes simplex type 1 virus or varicellae zoster virus could cause vestibular neuritis in a way that resembles Bells palsy and sudden unilateral hearing loss. Enhancement of the facial nerve on gadolinium-enhanced MRI is a common finding in Bells palsy and herpes zoster oticus. However, enhancement of the vestibular nerve has never been reported in vestibular neuritis. Here we report the findings of isolated vestibular nerve enhancement in two consecutive patients with vestibular neuritis, examined with 3.0 Tesla

MRI.

Methods. Vestibular and auditory tests: nystagmography an d caloric tests, subjective visual horizontal, vestibular evoked myogenic potentials, vestibular impulse test and audiometry. Neuroradiologic examination on a 3.0 Tesla head imager (Siemens Magnetom Allegra), with T1 sagittal, T2-flair axial and T2 coronal of the brain; and covering the internal auditory canal CISS axial and T1 axial (2 mm, TR 800, TE 15, matrix 192 X 256, 3 Acq) after standard dose Gadolinium-DTPA (0.1 mmol/kg body weight) and triple dose (0.3 mmol/kg body weight).

Results. A 66-years-old man woke with continuos rotatory vertigo and nausea. Investigations 3 days after onset of symptoms showed loss of function of the left superior and lateral semicircular canals and utricle with preserved function of the posterior semicircular canal and saccule, compatible with an isolated lesion of the left superior vestibular nerve. A 54-years-old woman fell suddenly ill with continuos rotatory vertigo, nausea and vomiting. Investigations 4 days after onset of symptoms showed loss of function of the right superior and lateral semicircular canals and utricle, compatible with a lesion of the right superior vestibular nerve. Seven and eleven days after symptom onset the respectve patients were examined in a 3.0 Tesla head imager. With standard doses of contrast agent no clear-cut pathologic findings were revealed. Triple-doses of Gadolinium-DTPA revealed enhancement of the left vestibular nerve in the man and of the right vestibular nerve in the woman. No abnormality of the nerves were found on the CISS images and there were no enhancements of the membranous labyrinths.

Conclusion. To the best of our knowledge, this is the first time that isolated contrast enhancement of the vestibular nerve has been visualized on MRI in patients with vestibular neuritis. These findings support the hypothesis of a local inflammation of the vestibular nerve or ganglion in vestibular neuritis. Previous MRI-studies of vestibular neuritis used lower contrast doses and field strengths. By increasing the field strength and contrast dose, the signal to noise ratio and sensitivity increase.

SP2.1
Dynamics of primate vestibular neurons during rotation
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The temporal processing in the encoding of head rotation was investigated by comparing the dynamics of vestibular nuclei neurons to those of the regularly- and irregularly-firing semicircular canal (SCC) afferents in alert rhesus monkeys.

During horizontal (yaw) rotations, Vestibular-Only neurons with no eye movement sensitivity (VO cells) differed in their response dynamics from both regularly and irregularly-firing SCC afferents. At high frequencies, central responses increased in sensitivity and maintained phase leads of nearly 300 deg relative to head velocity. These persistent high frequency phase leads resembled those of

irregularly-firing (but not regularly-firing) SCC afferents. However, at low frequencies, central responses exhibited significantly smaller phase leads than those of irregularly-firing SCC afferents and dynamics resembled more those of the regularly-firing afferents.

The response dynamics to yaw rotation were independent of the major canal input to the cell and whether or not it received orthogonal canal and otolith convergent inputs. The response dynamics of central VO cells were significantly different from those of horizontal Position-Vestibular-Pause (PVP) and Eye-Head (EH) neurons (collectively referred to as EM cells) during visual suppression. EM cells modulated closely in phase with head velocity at all frequencies down to 0. 05 Hz.

Vertical canal VO neurons that were insensitive to both translations and static head tilts led head velocity by approximately 30 deg during high frequency earth-horizontal axis rotations. Unlike the yaw-sensitive neurons that led head velocity at low frequencies by as much as 20-40 deg, vertical canal neurons only slightly led or even lagged head velocity at low frequencies. Posterior canal central VO cells lagged head velocity significantly more than anterior canal neurons.

The main features of these VO and EM response dynamics could be modeled by a first-order central processing stage that cascaded either regularly or irregularly-firing SCC afferent dynamics. The central processing model consisted of a neural integrator (potentially representing velocity storage) in parallel with a direct pathway of approximately equal strengths. A third, weaker pathway with high-pass filter characteristics was often also necessary in order to simulate the larger high frequency sensitivity increases and phase leads of central as compared to primary afferent neurons. The need for a high-pass filter pathway was particularly evident in a transformation of regularly-firing SCC afferent signals into central VO cell responses. Thus, central pathways contribute both low- and high-pass filtering in the rotational dynamics for the processing of vestibular afferent signals. (Supported by EY12814, DC04260, NAG2-1493 and NAG2-1204.)

SP2.2
Neural coding of 3D rotational and translational motion: convergence patterns of vestibular signals
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Sensory signal convergence is a fundamental and important aspect of brain function. Such convergence may often involve complex, multidimensional interactions, as proposed for the processing of otolith and semicircular canal (SCC) signals for the detection of translational head movements and the effective discrimination of gravity signals.

In the present study we have examined the responses of primate rostral vestibular nuclei neurons that do not exhibit any eye movement-related activity. These neurons were examined using 0. 5 Hz translational and rotational

motion. Two distinct neural populations sensitive to rotation were identified. One neuron population selectively encoded rotational movements (Canal-Only neurons) in SCC coordinates, exhibited little or no orthogonal canal convergence and was characterized with significantly higher sensitivities as compared to primary afferents. The second neuron population was sensitive to both rotations and translations (Otolith+Canal neurons), with rotational maximum sensitivity vectors that were scattered throughout the 3D space, in sharp contrast to Canal-Only cells. This second VN group appears to receive strong convergence from both otolith and multiple SCC pairs. Both populations exhibited larger sensitivities to motion as compared to primary afferents.

A quantitative comparison between response parameters during translation, as well as rotations with or without changes in orientation relative to gravity suggested that only a few convergent neurons (8/29, 28%) appropriately encoded the translational component of the movement. Neither were most of these convergent neurons, however, afferent-like in the sense that they encoded gravity equivalent to translational accelerations.

We propose that the Otolith+Canal convergent population represents the neural substrate for a distributed representation of translational motion, whereby decoding the population response or further processing would be required to correctly extract the translational component of the imposed movement. (Supported by EY12814, DC04260, NAG2-1493 and NAG2-1204.)

SP2.3
3-dimensional analysis of responses of vestibular neurons to translations and rotations
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We studied responses of 31 neurons in the vestibular nuclei of a trained squirrel monkey to sinusoidal 3-dimensional rotations (yaw, pitch, roll) and translations (Inter-Aural, IA; Naso-Occipital, NO; Dorso-Ventral, DV). At 1. 2 Hz two neurons responded primarily to rotations, 13 primarily to translations while 16 responded to both. This report focuses on 24 of our 29 translation-sensitive neurons that responded as well as or better to IA motion than they did to NO or DV motion. Nine of these were more than twice as sensitive to IA.

Ten of our IA neurons responded only to translation while 14 responded also to rotation. Six of the latter were also sensitive to eye position or eye velocity during smooth pursuit including four horizontal eye-head velocity (EHV) and one horizontal position-vestibular-pause (PVP) neurons. These neurons all carried linear or angular velocity signals during linear or angular VOR. When the angular VOR was cancelled by fixation, the PVP retained a large Type I response whereas modulation of EHVs reversed or shifted phase as expected. However, responses during the linear VOR always paralleled eye velocity, declining to near 0 during cancellation and increasing when LVOR gain was increased by viewing a near target.

When eye movement-related neurons are excluded, preferred directions of rotational and translational responses did not align as expected if otolith inputs activated by translation were serving to extend the low frequency range of responses to rotation. Response dynamics were diverse including 5 velocity, 5 acceleration, 5 hybrid (acceleration sensitivities/velocity phases) and 3 spatiotemporal convergent responses.

We also examined responses of 8 neurons that responded only to IA translations at 1. 2 Hz to 0. 3 Hz IA motion and roll tilt. Six were from 2 to 25 times as responsive to linear accelerations produced by translation as to accelerations related to changing head orientation with respect to gravity. Also, the response to roll was in the opposite direction to that predicted from responses to IA translation in 5/8 cases including the neurons with IA/roll ratios of 1. 5 and 0. 5. Thus translation-sensitive neurons in the vestibular nuclei have the capability of discriminating between otolith inputs produced by tilt and translation.

SP2.4
Characterization of vestibular nuclei afferents using transneuronal transport of pseudorabies virus
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The vestibular nuclei receive sensory information from a variety of sources, including the visual and somatosensory systems. In addition to the inputs originating from the labyrinths, these complementary signals are thought to aid in the calculation and determination of spatial localization and trajectory. Furthermore, it has been postulated that nonlabyrinthine inputs are important in maintaining spontaneous activity of vestibular nucleus neurons and even responses of these neurons to body rotations following loss of labyrinthine inputs. Characterization of inputs to the vestibular nuclei has previously been accomplished with a variety of conventional tracers and techniques. However the use of monosynaptic tracers only provided for the determination of direct inputs to the vestibular nuclei. The use of neurotrophic viruses that are transported transneuronally in a retrograde direction, has become an increasingly popular technique used to more extensively characterize multisynaptic circuits. In the present study, pseudorabies virus was used to determine the multisynaptic pathways that relay nonlabyrinthine inputs to the vestibular nuclei.

100-200 nl injections of pseudorabies virus were made into the vestibular nuclei of ferrets. Injections were confined to the medial vestibular nucleus, rostral inferior vestibular nucleus, and caudal region of Deiters' nucleus. After survival times of two to four days, infected neurons were localized in the raphe nuclei, nucleus tractus solitarius, dorsal motor nucleus of the vagus, prepositus hypoglossus, flocculus, reticular formation, inferior olive, temporal cortex, thalamus, cuneate and gracile nuclei, dorsal root ganglia, and the dorsal and ventral horn of the cervical, thoracic, and lumbar spinal cord. The labeling observed suggests that the vestibular nuclei are highly innervated

with synapses that provide somatosensory, visceral, and visual sensory inputs as well as motor feedback signals. These findings support the hypothesis that the vestibular nuclei integrate a variety of inputs that can be employed to determine body position in space.

SP2.5
Synaptic inhibition triggers long lasting increases in intrinsic excitability of vestibular nucleus
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Neurons of the vestibular nuclei have been shown to increase their firing rate during the process of vestibular compensation. Following lesions in the periphery, vestibular nucleus neurons lose their primary source of excitation, and inhibitory inputs such as those from the cerebellum might be expected to predominate. Making whole-cell and cell-attached patch recordings in mouse brainstem slices, we have found that following five minutes of high frequency inhibitory synaptic stimulation, the spontaneous firing rate of vestibular nucleus neurons increases by 30 to 50%. This increase in firing rate was stable over the course of the recording, up to two hours. In addition, the firing response gain (firing rate as a function of current injection) of vestibular nucleus neurons increased by 20%. Similar increases in firing rate and gain were observed when hyperpolarizing current injection or puffs of GABA were substituted for synaptic inhibition.

The phenomenon appears to be triggered by decrements in intracellular calcium and expressed as changes in the activity of BK large conductance calcium-activated potassium channels, as it was blocked by the selective BK antagonist, iberiotoxin.
Plasticity of intrinsic excitability may serve as a homeostatic mechanism allowing balanced activity to develop following unilateral damage to the vestibular system and contributing to behavioral recovery.

SP2.6
Ca++-dependent K+ channels are required for rapid increases in vor gain following vestibular damage
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The gain of vestibular nucleus neuronal responses is dictated in part by calcium-dependent potassium (K-Ca) channels. To determine whether adaptive control of the gain of the vestibulo-ocular reflex (VOR) depends on regulation of K-Ca channels, we investigated VOR plasticity in mice that had a temporally conditional (doxycycline-regulated) knockout of the SK3 K-Ca gene.

Eye movements were measured with an infrared video tracker while mice were either rotated on a turntable or stationary while viewing a rotating striped pattern.

Adaptive increases in VOR gain were induced with a unilateral damage to the vestibular labyrinth. Firing responses of medial vestibular nucleus (MVN) neurons were analyzed with intracellular current injection in brain slices.

Knocking out the SK3 gene had no effect on either the VOR or the optokinetic reflex, indicating that SK3 channels are not required for normal eye movements. In wildtype mice, unilateral damage to the vestibular labyrinth resulted in an immediate drop of VOR gain followed by an exponential increase in gain to ~80% of control values with a time constant of 5-6 days. The VOR in SK3 knockout mice increased to comparable values following unilateral labyrinthectomy. However, the time course of the gain increases in SK3 knockouts was slowed, such that the time constant of recovery was 15-20 days. Firing response gains of MVN neurons assessed with intracellular current injection were significantly higher in SK3 knockout mice than in wildtypes; however, the lowest gains were comparable, indicating that not all MVN neurons express SK3 channels.

We conclude that (1) behavioral gain control in the VOR is not achieved through regulation of SK3 K-Ca channels in MVN neurons, and (2) absence of SK3 channels impairs the error signals that are responsible for adaptive increases in VOR gain.

SP2.7
Vestibular compensation: a top-down hypothesis
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Vestibular compensation for the postural and oculomotor deficits following unilateral labyrinthectomy is a model of functional plasticity in the brain of adult vertebrates. The mechanisms involved in this recovery are still controversial. The post-lesional lack of vestibular input might be compensated by changes in the efficacy of the remaining sensory inputs involved in gaze and posture stabilization. However, the compensation process could also rapidly become independent of these external cues, and thus be detectable in vitro in preparations obtained from lesioned animals.

In agreement with that hypothesis, we have recently shown that prominent traces of the compensation process appeared three days after the lesion on in vitro isolated brains taken from labyrinthectomized guinea-pigs, where the connectivity of the central vestibular-related networks is preserved. One week after the lesion, a slight increase in the intrinsic, spontaneous activity of the deafferented, central vestibular neurons was found in brainstem slices. This increase became stronger in slices taken after one month of compensation.

At this stage, we characterized the static and dynamic membrane properties of deafferented vestibular neurons recorded intracellularly in guinea-pig brainstem slices. We compared the responses of the type A and type B cells identified in vitro to current steps and ramps, and to sinusoidal currents of various frequencies. All deafferented vestibular neurons were depolarized by 6-10 mV compared

to the cells recorded from control slices. Both their average membrane potential and firing threshold were increased, which suggests that changes in active conductances compensated for the loss of excitatory afferents. The proportion of type A neurons and the after-hyperpolarisation of the remaining type B neurons were significantly increased, both of which should stabilize the tonic discharge recovered in the deafferented nucleus. The deafferented type B cells became more sensitive to current injections over a large range of frequencies (0. 2-20 Hz), which might underlie the partial compensation of the dynamic vestibular reflexes observed in vivo. This was associated with an extension of the linear frequency response range of type B neurons, which might reduce their capacity to act as non-linear signal detectors and thus explain why responses to high amplitude velocity steps stay permanently impaired in lesioned animals. At one month post-lesion, there was also a significant decrease in the intrinsic activity of the vestibular neurons on the contralesional side.

Vestibular compensation could thus follow a "top-down" strategy: it would first rely on the external cues given by the intact sensory systems, then on an internal reorganization of the vestibular-related networks, and finally on changes in the intrinsic properties of the vestibular neurons themselves. Similar strategies may be used by the mammalian brain to compensate for other types of deafferentations or environmental changes.

SP2.8

Acetyl-DL-leucine effects on vestibular neurons explains its efficacy during vertigo crises
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For more than 40 years, high doses of acetyl-DL-leucine (Tanganil®) have been successfully used in clinical practice to treat acute vertigo crises without generating strong side effects. However, the mechanisms underlying this action of acetyl-DL-leucine are still unknown. Acetyl-DL-leucine was shown to accelerate behavioral compensation following unilateral labyrinthectomy in cats, but has only minor effects on normal vestibular function in humans.

The effects of acetyl-DL-leucine on central vestibular neurons (VNn) were first assessed in brainstem slices taken from normal guinea pigs. Only moderate effects were obtained using concentrations similar to those reached in the blood in clinical practice. However, we could demonstrate that acetyl-DL-leucine had significant depolarizing effects on the VNn that had a more hyperpolarized than normal mean membrane potential, and significant hyperpolarizing effects on the neurons with a more depolarized than normal membrane potential. Altogether, acetyl-DL-leucine tended to bring back all VNn towards a normal mean membrane potential of about – 60 mV.

To check this hypothesis, we compared the effects of acetyl-DL-leucine obtained on isolated, in vitro whole brains (IWBs) taken from normal animals with those ob-tained on IWBs taken from previously labyrinthectomized animals. In control IWBs, the level of activity and membrane potential of VNn is similar on both sides of the brainstem, with a mean membrane potential value close to – 60 mV. In contrast, the level of activity of VNn is highly asymmetric between both sides of the brainstem on IWBs taken from previously labyrinthectomized animals (Vibert et al. 1999, Neuroscience 93: 413-432). In accordance with our hypothesis, acetyl-DL-leucine had only moderate effects on IWBs taken from normal animals, but strongly reduced the asymmetry characterizing the vestibular-related networks of IWBs taken from previously labyrinthectomized animals. Acetyl-DL-leucine acted mainly by inhibiting the abnormally depolarized neurons on the hyperactive side, but tended also to activate the abnormally hyperpolarized neurons on the hypoactive side.

In a last step, we undertook an in vivo study to quantify the effect of acetyl-leucine on vestibular compensation in the guinea pig. Administration of acetyl-DL-leucine induced a significant decrease of the spontaneous ocular nystagmus and horizontal head deviation induced by unilateral labyrinthectomy, beginning in the first few hours of compensation. The effect of the drug was maximal in the second and third days following the lesion.

Altogether, acetyl-DL-leucine seems to act almost exclusively on abnormally polarized central vestibular neurons by bringing back their membrane potential towards its normal value close to -60 mV. Since in animal models, acute vestibular disorders are associated with strong asymmetries in central vestibular networks, these data suggest how acetyl-DL-leucine could reduce vestibular-related imbalances in humans. Indeed, acetyl-DL-leucine would at the same time activate the hypoactive VNn on the lesioned side and suppress the hyperactivity of VNn on the contralesional side, thus strongly reducing the imbalance between the activity of central vestibular networks on both sides of the brainstem.

SP3.1

Vestibular climbing fibers modulate simple spikes in cerebellar purkinje cells
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Purkinje cells have two action potentials: Climbing Fiber Responses (CFRs) and Simple Spikes (SSs). CFRs reflect the discharge of a single climbing fiber at multiple synaptic sites on the proximal dendrite of the Purkinje cell. SSs reflect the summed action of a subset of parallel fiber synapses on Purkinje cell dendritic spines. Since mossy fiber afferents terminate on granule cells, whose ascending axons bifurcate, giving rise to parallel fibers, the modulation of SSs has been attributed to mossy fiber afferent signals. This inference has never been tested. Conversely, the low discharge frequency of CFRs has led many to conclude that CFRs have a unique, if intermittent, role in cerebellar signal processing. It would be possible to examine how Purkinje cell discharge is regulated by cerebellar circuitry, if it were possible to examine independently the signals

carried by mossy fiber and climbing fiber afferents to the same region of the cerebellum. This independent manipulation of mossy fiber and climbing fiber signals is possible to achieve in the nodulus. The nodulus receives a major vestibular primary afferent mossy fiber input from the ipsilateral labyrinth. It also receives a vestibular climbing fiber input that originates from the contralateral labyrinth. A unilateral labyrinthectomy (UL) should eliminate the vestibular primary afferent mossy fiber input while preserving the vestibular climbing fiber input. Conversely, a unilateral lesion to the beta nucleus of the inferior olive should reduce the climbing fiber input to the contralateral nodulus without disrupting the vestibular primary afferent mossy fiber input.

We examined the effects of manipulating these two signals independently. After a UL, vestibularly-modulated SSs and CFRs could still be recorded ipsilateral to the UL. The SSs were antiphasic to the CFRs, as they are in intact rabbits. Modulated CFRs were recorded contralaterally to the UL, but there relative efficacy in modulating SSs was reduced. After microlesions of the beta nucleus of the inferior olive, CFRs were reduced in the contralateral uvula-nodulus. SSs recorded from Purkinje cells that lacked a CFR or had an unmodulated CFR, also had SSs that were not modulated. The enigma posed by the apparent irrelevance of CFRs to signal processing in the cerebellum is contradicted by our findings. Climbing fibers not only evoke CFRs, but also determine the topography and polarity of SSs. (Supported by NEI EY04778.)

SP3.2

Optokinetic stimulation modifies transcription of two gene products in floccular Purkinje cells
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Long-term, binocular optokinetic stimulation (OKS) in rabbits causes progressive decreases in gain of the optokinetic reflex and evokes optokinetic afternystagmus (OKAN II) when OKS is stopped. OKS increases climbing fiber discharge to one flocculus and decreases it to the other. The rabbit flocculus has three easily identified folia. These can be removed without inclusion of non-floccular cerebellar cortex. Consequently, it is possible to compare changes in the flocculus that are specific for changes in the optokinetically-induced change in activity. Transcriptional changes may account for some of the observed plastic oculomotor behavior. These were studied using "differential display. "

Rabbits received binocular OKS for 48 hours. Subsequently, they were anesthetized and the two flocculi were removed. Total RNA was extracted and prepared for "differential display. " Differentially transcribed gene products were re-amplified by PCR and sequenced. Two differentially transcribed gene products isolated by this technique were: Calbindin and 14-3-3-protein-theta mRNA. Both were elevated in the flocculus receiving reduced climbing fiber input. The identities of calbindin and 14-3-3-protein-theta mRNAwere confirmed with Northern blots and semi-quantitative RT-PCR. Both have been sequenced.

Western blots showed that calbindin is found in the cytosolic fraction while 14-3-3-protein-theta is found in both cytosolic and membrane associated fractions. Hybridization histochemistry with oligonucleotide probes further localized the transcripts to Purkinje cells. The localization of calbindin and 14-3-3-protein-theta to Purkinje cells was confirmed immunohistochemically using specific monoclonal antibodies. OKS reduced calbindin mRNA could be detected only in the population of Purkinje cells localized to folium 1. Similarly, the immunohistochemical measurement of differences in reaction product density were only significant for the subset of Purkinje cells restricted to folium 1. . Four other calcium-binding proteins (calmodulin, S-100 protein, calretinin and parvalbumin) are expressed in Purkinje cells, but not influenced by OKS. 14-3-3-protein- is a member of a conserved family of proteins implicated in intracellular signaling that involves protein kinases and phosphatases as well as other regulatory proteins.

In Purkinje cells, activity-dependent expression of 14-3-3-protein-theta could alter efficacy of the constitutively expressed isoforms of protein kinase C (PKC-gamma and PKC-delta). These two PKC isoforms have also been localized to Purkinje cells. One of them, PKC-gamma, belongs to the calcium-dependent class of PKC isoforms. It is possible that both calbindin and 14-3-3-protein-theta alter intracellular signaling by PKC-gamma either directly (14-3-3-protein-theta) or indirectly (calbindin) by influencing intracellular concentration of calcium. (Supported by: NIDCD DC02557)

SP3.3

Impaired spatial memory of vestibular and optokinetic stimulation in rabbits following nodulectomy
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Natural vestibular and optokinetic stimulation were used to investigate the possible role of the cerebellar nodulus in the regulation and modification of reflexive eye movements in rabbits. Folia 9d and 10 were destroyed by surgical aspiration.
 1) Does the nodulus influence vestibuloocular reflex gain? Before and after nodulectomy, vertical and horizontal vestibuloocular reflexes (VVOR, HVOR) were measured during sinusoidal vestibular stimulation. The gain of the VVOR was reduced by the nodulectomy. The gain of the HVOR was not.
 2) Does the nodulus contribute to optokinetic reflex gain? Gains of the vertical and horizontal optokinetic reflexes were measured during monocular, sinusoidal optokinetic stimulation (OKS). There was no change in the gain of either optokinetic reflex.
 3) Is the plane of nystagmus influenced by head position equally before and after nodulectomy? Long-term binocular OKS was used to generate optokinetic afternystagmus (OKAN II). Unlike vestibular nystagmus, OKAN II has

the advantage that it persists for several hours at a constant velocity once it is induced. Rabbits were pitched and rolled statically to determine how the plane and velocity of OKAN II was influenced by altering head position with respect to the linear acceleration of gravity in post-nodulectomized rabbits. During static pitch, OKAN II slow phase remained aligned with earth-horizontal in normal and nodulectomized rabbits. In nodulectomized rabbits, OKAN II slow phase had a centripetal vertical drift.

4) Can the optokinetic suppression of vestibuloocular reflex gain be attributed to the nodulus? We examined the suppression and recovery of the gain of the VVOR after conflicting vertical OKS for 10-30 min. This vestibular-optokinetic conflict reduced the gain of the VVOR in both normal and nodulectomized rabbits. The time course of recovery of the gain of the VVOR was the same before and after nodulectomy.

5) Could the nodulus influence higher order variables such as "remembered" head position? In normal rabbits, the head pitch angle (HPA) maintained during long-term OKS determines the HPA at which peak OKAN II velocity is subsequently recorded. If the head is maintained in a "pitched-up" or "pitched-down" orientation during long-term OKS, the subsequently measured OKAN II peak velocity occurrs at the same orientation. This was not true for nodulectomized rabbits. They had peak OKAN II velocities at HPAs that were independent of those maintained during long-term OKS.

Conclusion. The nodulus participates in the regulation of compensatory reflexive movements in the vertical plane. The nodulus also influences "remembered" head position in space, derived from previous optokinetic and vestibular stimulation. (Supported by NEI EY04778.)

SP3.4

A VVOR deficit reveals combined bilateral vestibulopathy and cerebellar dysfunction
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Both visual (smooth pursuit (SP) and optokinetic (OKR) tracking) and vestibular reflexes (VOR) contribute to gaze stabilization for head movements up to about 1Hz. These combined, compensatory eye movements have been called the visual vestibulo-ocular reflex or the VVOR. To better understand the interaction between visual and vestibular reflexes when generating compensatory eye movements we tested each reflex independently and in combination with the other at different frequencies. Eye and head rotations were measured using magnetic search coils. The horizontal VOR was tested by measuring eye rotations in response to passive sinusoidal yaw head rotations in total darkness; SP was tested by measuring horizontal eye rotations while trying to fix a laser target moving sinusoidally in the horizontal plane; combined VOR and SP was tested by measuring eye rotations in response to yaw head rotations while fixing a stationary laser target. The frequencies

of head and target movement were 0. 1, 0. 3, 0. 6 and 1. 0Hz.

We tested 5 normal subjects and 6 patients. Four patients had bilateral vestibular hypofunction as evidenced by gain less than 0. 2 for responses to passive, high acceleration head impulses in the excitatory direction for each of the horizontal canals. Additionally, these patients had impaired SP+OKR tracking but normal saccades. One patient had normal vestibular function but impaired SP+OKR, whereas another patient had impaired vestibular function but normal SP+OKR.

The results showed that patients with impairment of both SP+OKR and VOR can nonetheless produce an eye velocity that approximates head velocity at 0. 1 and 0. 3Hz, indicating that there is summation of the residual SP+OKR and VOR at the lower frequencies. In contrast with increasing frequency of head rotation (0. 6 and 1. 0Hz), eye velocity increasingly fails to match head velocity so that gaze velocity increases. The gaze position errors that develop during the head movement are then corrected with a burst of saccade-like eye movements that are readily apparent on clinical examination. In contrast, for those subjects with VOR or SP+OKR impairment only the VVOR response was the same as that observed in normal subjects. The major findings of this study are that: (a) a VVOR deficit reveals a combined bilateral vestibulopathy and cerebellar dysfunction; (b) a VVOR deficit can be detected with head-fixed testing in a rotating chair, and (c) a VVOR deficit can even be detected with bedside head free-testing by observing bursts of compensatory saccades during head turning.

SP3.5

Muscarine-induced enhancement of spontaneous EPSCS in Purkinje cells in the rat vestibulo-cerebellum
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Choline acetyltransferase is densely distributed in the vestibulo-cerebellum. We examined effects of acetylcholine (ACh) on electrical activities of both Purkinje cells and granule cells in this region in rat vermal slices using whole-cell patch-clamp technique. Bath application of ACh produced a long-lasting increase in frequency of spontaneous EPSCs (sEPSCs) in Purkinje cells. Muscarine also induced the enhancement of sEPSCs in a dose-dependent manner with an EC50 of 0. 287 mM. These effects of ACh and muscarine were blocked almost completely by 4-diphenylacetoxy-N-methylpiperidine methiodide (4DAMP), a muscarinic M3 receptor antagonist. The muscarine-induced enhancement of sEPSCs was prominent in the lobules IX, X, but only rarely seen in the other lobules. Tetrodotoxin (TTX) suppressed this facilitatory effect of muscarine on Purkinje cells, suggesting that muscarine acts on Purkinje cells indirectly through the excitation of presynaptic neurons.

We therefore investigated the effect of muscarine on

granule cells in the lobule X using perforated-patch clamp technique. In current-clamped granule cells, muscarine elicited membrane depolarization of 8.3 ± 3.0 mV (n = 19) accompanied by a reduction of the membrane conductance, and thereby increased their firing frequency. Furthermore, in approximately 15% of granule cells (15 out of 81 cells tested), the standing-outward K+ current (IKSO) at -30 mV was partially blocked by muscarine, and this blockage was abolished by 4-DAMP.

We conclude that muscarine enhances the excitation of granule cells by inhibiting IKSO, which in turn increases the frequency of sEPSCs in Purkinje cells, and that these muscarine-induced events occur specifically in the vestibulo-cerebellum.

SP3.6

Changes in head-on-trunk position influence vestibular responses of fastigial nucleus neurons

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The vestibular system helps to stabilize the body by generating reflectory contractions in trunk- and limb muscles in response to perturbating head movements. This requires complex sensorimotor interactions: as the body assumes different positions relative to the head, different sets of muscles need to be activated in response to identical vestibular stimuli. Consequently, information about body position must be incorporated in the generation and adequate distribution of vestibulo-spinal reflex activity. Where, and how, this sensorimotor integration is achieved, is largely unknown.

Recent evidence suggests that the cerebellum may be involved: Manzoni et al. (1998) showed in decerebrate cats, that the preferred orientation of triceps-motoneurons responding to activation of labyrinthine receptors shifted with the trunk, when the body was displaced relative to the head, and that this compensatory shift was reduced after pharmacological inactivation of the anterior cerebellar vermis. Moreover, vestibular Purkinje cells in this vermal region also shifted their preferred response orientations after body re head displacement (Manzoni et al. 1999). The rostral fastigial nucleus (rFN) is target zone of the Purkinje-cell-output of the anterior vermis. It is reciprocally connected to the vestibular nuclei and also projects directly to the spinal cord. Vestibular neurons in rFN have therefore been implicated in vestibulospinal mechanisms, but their precise functional role is unknown.

To study the influence of proprioceptive neck inputs on vestibular responses in rFN neurons, alert monkeys were subjected to vertical vestibular stimulation (0. 1-1 Hz). Trunk position (+- 45° re head) was controlled by an individually molded corselet attached to a platform which could be rotated about an axis passing through the dens of the atlantoaxial joint. At each trunk orientation, units were tested at 2 orthogonal stimulus orientations (roll and pitch), allowing to calculate the response parameters for all intermediate vertical stimulus directions (Kleine et al. , 1999). Changes in head-on-trunk position influenced the spatio-

temporal properties of most vestibular rFN units. Most neurons exhibited shifts of their preferred orientation which (partly) compensated for the altered head-on-trunk-position (~75% on average). These findings strongly indicate that the FN participates in the sensorimotor transformations required to account for changes in the relative position of the labyrinths and the body.

SP3.7

Gravity-dependence of ocular drift in patients with cerebellar downbeat nystagmus

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Downbeat nystagmus (DBN) is a frequent ocular motor sign in patients with lesions of the vestibulo-cerebellum. The upward drift in DBN is a combination of a gaze-evoked drift, due to an impaired vertical neural integrator (gaze-holding network), and a velocity bias. Using a three-dimensional motorized turntable, we analyzed the influence of gravity on these two mechanisms.

Patients with cerebellar DBN (N=6) and healthy subjects (N=12) were placed in different whole-body positions along the roll, pitch, RALP (right ear anterior, left ear posterior), and LARP (left ear anterior, right ear posterior) planes of the head. Ocular drift was monitored with scleral search coils. While there was no gravity-dependence of the vertical gaze-evoked drift, the vertical velocity bias consisted of two components: (1) a gravity-dependent (GD) component that sinusoidally modulated as a function of body position along the pitch plane, and (2) a gravity-independent (GI) component that was always directed upward. The combination of the GD- and GI-component led to an overall drift that was minimal in supine position and maximal in prone position. In healthy subjects, only the GD-component was present, but in a scaled-down manner.

Our results suggest that the intact vestibulo-cerebellum minimizes an overacting otolith-ocular reflex elicited by pitch-tilt and cancels an upward ocular drift that is independent of gravity-modulated otolith signals. (Supported by Swiss National Science Foundation (32-51938. 97 / 31-63465. 00) and Koetser Foundation for Brain Research, Zurich, Switzerland).

SP3.8

Context dependent signal processing in the cerebellar flocculus and ventral paraflocculus during gaze saccades

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The flocculus and ventral paraflocculus (F-VPF) participate in gaze stabilization during compensatory eye movements produced when the head is passively rotated in space. The firing rates of Purkinje cells in the F-VPF are modulated during the compensatory eye movements produced by the VOR, and their output modifies signal processing in central VOR pathways. The eye movements

produced during saccadic eye-head gaze shifts are composed of a rapid eye movement in the direction of the gaze shift and a compensatory, rollback VOR eye movement that stabilizes gaze once the target has been acquired on the fovea. F-VPF Purkinje cells are not consistently sensitive to eye velocity during ocular saccades and their firing rate is never related to gaze velocity during eye-head saccades (Belton and McCrea 2000). In the present study we analyzed the firing behavior of squirrel monkey F-VPF Purkinje cells during the compensatory rollback VOR eye movements that accompany gaze saccades.

In monkeys two types of Purkinje cell are found in the F-VPF. Eye velocity Purkinje cells (≈50% of the population in the squirrel monkey) generate signals related to eye velocity and dynamic eye position during the VOR when the head is moved passively. But these cells did not fire in relation to the compensatory rollback eye movements that accompanied gaze saccades. This was true whether the saccade was made to a visual target or spontaneously generated in the absence of a visual target in the dark. Eye-head velocity Purkinje cells (the other 50% of the population) generate signals that are related both to smooth eye velocity and to head velocity in space during passive and smooth tracking head movements. Most of these cells were insensitive to eye and head movements during the rollback VOR, although some (≈40%) generated a burst of spikes during the rollback VOR when the compensatory eye movements were in the cell's on direction.

In summary, F-VPF eye velocity feedback input to VOR pathways is largely removed during the rollback eye movements that accompany gaze saccades. The removal of this inhibitory input may help compensate for the addition of neck reafferent and head movement efference copy inputs to VOR pathways during active saccadic head movements.

SP3.9
Eye-, head- and gaze-movement during horizontal and vertical gaze pursuit in SCA6

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In daily life, we obtain visual information from slowly moving objects using coordinated movements of eyes and head. Lanman et al. (1978) suggested that such gaze (eye+head) pursuit is produced by a common drive that interacts with the vestibular system to override the vestibulo-ocular reflex (VOR). Neural recording (Lisberger et al. 1978, Suzuki et al. 1988) and lesion studies (Zee et al. 1981, Robinson et al. 1997) in monkeys have implicated the cerebellum in control of smooth eye movements but

less is known about gaze pursuit with head unrestrained.

To clarify the role of cerebellum in coordination of eye and head movements, we studied smooth gaze tracking with head restrained and unrestrained in patients with an autosomal dominant pure cerebellar ataxia (SCA6).

Six SCA6 patients participated in this study and their results were compared with those of age-matched normal controls. Subjects sat on a chair facing a vertical screen. Chair rotation was applied only horizontally. Laser spot target and/or chair were moved sinusoidally at 0. 2 or 0. 5 Hz (±10°). Subjects tracked the target either with head free or head restrained to the chair. Infrared oculography was used to record horizontal and vertical eye movements. Subjects wore a helmet to which a search coil was attached to record horizontal and vertical head movements. A small laser projector (i. e. head laser) was also attached to the helmet to give subjects visual feedback of head position.

Three tasks were tested with head restrained: smooth pursuit, VOR-cancellation and VOR in darkness. During VOR cancellation, a chair-fixed laser projector was used to present a target that moved in-phase with the chair with the same direction and amplitude. During head free pursuit, subjects were asked to track the target under three different head motion conditions; 1) to track the target in their most comfortable way (comfortable task); 2) to pursue the target spot with the head-laser spot (head-laser task); and 3) to track the target mainly using head movement (use-head task). Eye-, head-, gaze- gain and phase shifts relative to stimulus velocity were calculated in each task.

All SCA6 patients showed severe impairment of smooth pursuit. The most severely effected patients also had difficulty with VOR cancellation but this deficit was not significant across the population. Neither normals nor patients used large head movements to track the ±10° target motion in the comfortable condition even though this meant that patients employed saccadic eye tracking. During head free pursuit with the head-laser and use-head conditions, patients showed high head-gains (mean 1. 08) which were opposed by backward eye movements (mean 0. 41) resulting in smooth gaze movements too small to stabilize the target. Normals never exhibited such opposing eye-head movements in the head laser task but some did so in the use head task. In either case, the summed gaze movements were close to target velocity.

These results suggest that cerebellar dysfunction in SCA6 did not impair smooth head tracking itself but did impair gaze tracking through disordered eye-head coordination.

SP4.1
Recovery of the high-acceleration vestibulo-ocular reflex after vestibular neuritis

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Vestibular neuritis (VN) usually leads to a sudden asymmetry of the horizontal vestibulo-ocular reflex (VOR). Some degree of asymmetry can still be detected by high-acceleration rotation of the head after many months. We

asked whether in patients after VN the asymmetry of high-acceleration horizontal VOR decreases over time due to peripheral recovery and / or central compensation.

The horizontal VOR during rapid rotational head impulses to both sides was recorded with search coils in 37 patients at different time periods (1-240 weeks) after the onset of VN. In ten patients, sequential measurements were performed. Gains of the VOR during head impulses towards the weaker side significantly increased after a few weeks (average gains: < 1 week: 0. 35; 1-4 weeks: 0. 33; 4-40 weeks: 0. 55; 40-240 weeks: 0. 50). Gains on the stronger side, however, were only slightly reduced and showed no significant change over time.

We conclude that, in contrast to patients after hemilabyrinthectomy or unilateral vestibular neurectomy, vestibular function on the weaker side in patients after VN improves over time. This indicates that at least part of the recovery is peripheral. Considering the physiology of linear and non-linear VOR-pathways (Lasker, Hullar and Minor 1999), the relatively high gain during contralateral head impulses can best be explained by central upregulation. Thus, for high accelerations of the head, effective central compensation does not aim to balance the gains of the VOR, but, in fact, is the main source of VOR-asymmetry.

SP4.2

Normal performance and the expression of learning in the vestibuloocular reflex at high frequencies

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The vestibuloocular reflex (VOR) helps keep the world stable on the retina during head movements by effecting eye velocities that are equal in amplitude and opposite in direction to head velocity. Perfect gain, defined as eye velocity divided by head velocity, would be one, and the phase difference between eye and inverted head velocity should be zero degrees. The VOR is thought to be mediated by two pathways; one that changes as a result of lens-induced adaptation (modifiable pathway), and one whose output does not (unmodified pathway; Lisberger 1984).

This study was designed to further distinguish between the modified and the unmodified pathways by testing across a wide range of frequencies of head velocity. VOR responses to sinusoidal head velocity inputs with frequencies up to 50 Hz were obtained from two monkeys. Data were obtained in the dark under normal conditions, and after adaptation with magnifying and miniaturizing goggles. Under normal conditions, VOR gains were close to one for frequencies up to 12. 5 Hz, but were smaller than one for frequencies up to 25 Hz and larger than one at 40 and 50 Hz. The phase difference between the eye and inverted head velocity was close to zero degrees up to 12. 5 Hz, but eye velocity lagged the phase of inverted head velocity at higher frequencies. After adaptation with magnify-

ing or miniaturizing lenses, the gains were increased or decreased at frequencies up to 25 Hz, but were unchanged from normal at higher frequencies. There was also a change in the phase difference between head and eye velocity at frequencies up to 25 Hz, but not at higher frequencies. The phase change was equivalent to a constant 5 ms lag or lead for increases and decreases in gain, respectively.

These results suggest that the modified VOR pathways do not respond to vestibular input at frequencies above 25 Hz.

SP4.3

Short-term adaptation of the VOR: role of non-retinal slip error signals and saccade substitution

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Adaptive plasticity of the vestibulo-ocular reflex (VOR) is primarily driven by retinal-image motion during head movements. Using search coils, we studied VOR adaptation without retinal-image motion in four normal humans. The vestibular stimulus was a 15deg chair rotation in darkness (43deg/s peak vel). For each subject, we performed two experiments on separate days. One experiment aimed to reduce and the other to increase the VOR gain. During an experiment, each trial began with fixation of an LED directly in front of the subject that went off when the chair began moving. For test trials (40 each before and after training), the LED reappeared in its original position when the chair stopped. Subjects were instructed to fix on the imagined location of the LED during rotation. During training (350 trials, 30 min), the LED appeared in a new position, either directly in front of the subject (decrease paradigm) or 10deg opposite head motion (increase paradigm). Subjects were told to move their eyes smoothly during rotation to end up looking at the location of the final LED.

For each subject, in both experiments, VOR position gains (ratio of total eye movement during chair rotation to amplitude of rotation) changed significantly in the predicted directions (mean 5% for increase and 11% for decrease paradigm). VOR velocity gains (at peak head velocity) decreased significantly (6%) in the decrease paradigm but increased non-significantly in the increase paradigm experiments. Interestingly, during adaptation there were often combinations of one-upon-the-other, saccade-like movements that together resembled the desired slow-phase response. These results further emphasize the role of non-retinal slip error signals and saccade substitution in VOR adaptation.

SP4.4

Adaptation of the response to head heaves, surges and thrusts

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Many studies have investigated adaptation of the VORs in response to sinusoidal stimulation. We have be-

gun investigations on adaptation of the VORs in response to brief, high-acceleration, small-amplitude head motions (rotational "thrusts," inter-aural "heaves," fore-aft "surges"). These stimuli are more analogous to the head movements that occur in natural behavior, and the oculomotor response to each movement is less affected by more volitional contributions and predictive pursuit. This work explores the hypothesis that the demands of the different VORs (foveal positioning for TVOR versus full-field velocity for AVOR) will be reflected in both the error signals that drive adaptation of each response (foveal/peripheral, position/velocity), and in the form that the adaptive response takes in each case (change in smooth component velocity, contribution of saccades).

Experiments on heaves, surges, and thrusts were conducted, using a visual-vestibular mismatch to induce adaptation of the angular or translational VOR (AVOR, TVOR). To decrease gain, the visual target was head-fixed (x0). To increase gain, the target moved in the direction opposite to head motion by the same amount (x2). For each of these types of adaptation, the error signaling that a change in VOR was needed could be either velocity (target remains illuminated during head motion) or position (target is extinguished during head motion and presented again when the head stops). Responses were assessed by comparison with an ideal compensatory response, which was calculated based on head movement and initial target position. Velocity gains were found at peak head velocity, and position gains were found as total eye excursion (including saccades) relative to ideal. Particular attention was paid to the role of saccades in the response before and after adaptation.

Results show that all three responses (heaves, surges, thrusts) can be adaptively modified in at least some paradigms. With heave responses, position gains are higher and more adaptable than velocity gains, reflecting the importance of saccades in the response and in the adaptation. After gain-increase adaptation, saccades occurred earlier in each response and were also larger. Little or no transfer of adaptation to the AVOR was noted. Surge responses also exhibited more consistent changes in position that velocity gains. Forward surges had overall higher gains than backward surges. Thrusts were also adaptable, and adaptation imposed with passive thrusts transferred to active thrusts. (Supported by NIH DC02849 and NASA/NSBRI.)

SP4.5

An investigation of the angular vestibuloocular reflex at very high frequencies using a prosthesis
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We have developed a neural vestibular prosthesis to electrically stimulate the ampullary nerve in the lateral semicircular canal of animals. The prosthesis provides electrical stimulation using charge-balanced biphasic current pulses, and the modulation of the pulse rate upward and downward mimics the semicircular canal's normal signaling scheme. Head angular velocity is encoded by a proportional change in the prosthesis pulse rate, compared to the pulse rate when the subjects are stationary. Each canal receiving electrical stimulation is plugged, in order to prevent mechanical motion from confounding the prosthesis stimulation.

When head angular velocity has been communicated to the subjects via the prosthesis, compensatory eye movements have been observed, consistent with the normally functioning angular vestibuloocular reflex (AVOR). Our neural vestibular prosthesis offers the opportunity to study the AVOR at frequencies impractical to achieve via motion. We used this opportunity to investigate the frequency response of the AVOR and characterize the gain and phase between 1 and 150 Hz.

In order to avoid confounding nonlinear effects, the prosthesis stimulation for these experiments was designed to consist of periods of stimulation at a constant stimulation rate (pulse rate) and periods of no stimulation. In other words, stimulation consisted of square waves (1 to 159 Hz) that modulated biphasic current pulses applied with a pulse rate between 50 and 5000 Hz.

Spectral results showed eye responses at frequencies that were odd harmonics of the modulating square wave. The responses at the fundamental frequency had the highest signal-to-noise ratio. Therefore, these were used to derive response gain and phase. Gain was roughly constant, within 60 percent, with no trend evident across a frequency span greater than two decades, from 1 to 150 Hz. The phase plots were incrementally linear from 1 to 150 Hz, with slopes corresponding to delays in the range from 8 to 13 msec, consistent with the known latency of the elementary AVOR. (Supported by: DC-03066)

SP4.6

VOR adaptation reveals signals modulating gain control for smooth pursuit eye movements
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Previous studies from our laboratory have demonstrated that smooth pursuit eye movements are subject to gain control: eye velocity responses to high frequency perturbations of target velocity are enhanced during ongoing pursuit relative to during fixation.

To analyze the signals involved in the modulation of pursuit gain control in monkeys, we probed the gain of the visuo-motor transformation for pursuit during ongoing steps of target and head velocity before and after adaptation of the vestibulo-ocular reflex (VOR). Before VOR adaptation, the degree of enhancement of gain control varied with gaze (eye + head) velocity, or target velocity in space. Eye velocity responses to single-cycle sine wave perturbations of target velocity (10 hz, +/- 5 deg/s) were smallest during the VOR, where gaze velocity is zero. Responses became more enhanced as gaze velocity increased, whether the target was moving in the same or opposite direction as the head (ie, decreasing or increasing eye velocity). After spec-

tacle-induced increases or decreases of VOR gain, perturbation responses generally declined for combinations of target and head velocity that approximated the new VOR gain. However, the combinations of head and target velocity that resulted in the smallest perturbation responses were not those that exactly mimicked the adapted VOR gain, but rather, those representing an intermediate between normal and adapted gains.

We conclude that online gain control for smooth pursuit eye movements is modulated by a combination of signals related to both gaze-velocity-in-space and target-velocity-relative-to-VOR. (Supported by: HHMI, NIH)

SP4.7
Anticipatory VOR suppression in humans during repeated cued head movements
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Previously it has been shown that anticipatory ocular pursuit responses can develop with repeated presentations of a single-cycle sinusoidal visual target if each presentation is preceded by a regularly timed auditory warning cue. Here we examined whether similar anticipatory eye movements occur during visual and non-visual suppression of the vestibulo-ocular reflex (VOR). Subjects were exposed to repeated single-cycle sinusoids of head velocity (50deg/s peak, 1 or 2s period), with random intervals of at least 3s between stimuli. Four basic conditions were examined, in each of which the motion stimulus was normally preceded by an audio cue 400ms before onset. In the 'VOR' condition no target was presented during head motion and a compensatory response (mean gain 0. 62) was generated. In the 'HFT' condition a head-fixed target appeared during the period of head motion. After one or two presentations, anticipatory VOR suppression developed. This resulted in an initial period, prior to the start of head movement, in which smooth eye movements occurred in the same direction as head movement (i. e. opposing the subsequent VOR). If, at unexpected intervals, the target failed to appear, an anticipatory response was initiated that was identical to that when the target was presented. In contrast, when no audio cues were given, no anticipatory responses arose, and VOR suppression did not start until at least 100ms after head motion onset. In the 'IHFT' condition no target was presented but subjects were instructed to fixate an imagined head-fixed target. With audio cues, anticipatory eye movements appeared as in HFT trials, whereas without cues, VOR suppression did not start before motion and was less effective than in the cued condition for at least 400ms. In cued smooth pursuit ('SP') trials, anticipatory eye movements were initiated as observed in previous experiments. The similarity of anticipatory movements in SP and HFT conditions reinforces the notion of a common underlying process. The presence of anticipatory smooth eye movements in the IHFT condition shows that the effect does not require prior visual motion information, but can be associated with prior head motion. This implies that vestibular

input can be utilized to provide a signal related to estimated "target" motion in connection with (or shared by) the smooth pursuit system.

SP4.8
Total sleep deprivation can increase vestibulo-ocular responses
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Few studies focus on the effect of sleep deprivation on the vestibular function. Moreover, their results are conflicting : some found decreased vestibular responses and some no modification. The aim of this study was to test the effect of sleep deprivation on the canal-ocular responses.

Vestibular ocular reflex was studied in 20 healthy subjects once after a normal night and once after a 24 hours sleep deprivation. There was a two week interval between the tests, half of the subjects started with the sleep deprivation and the other half with the control night. Horizontal and vertical eye movements were recorded by electronystagmography during earth vertical axis rotation in darkness. In a first experiment (n=8), the rotations were a clockwise and conterclockwise velocity steps of 60°/s. In a second experiment (n=12), the vestibular stimulation was a sinusoidal rotation test (±25 °/s, 0. 2 Hz, during 50 s). Quantified velocity step response parameters were the gain and the time constant. Responses to per-rotatory and post-rotatory stimulation were averaged. Sinusoidal rotation response parameters were the gain and the phase. We used paired t tests to compare the parameters in the two conditions (sleep deprivation or normal sleep).

After a total sleep deprivation, the gain of the velocity step (0. 90±0. 18) was significantly higher than after a normal sleep night (0. 77±0. 16) (p < 0. 005). We observed no effect of sleep deprivation on time constant (11. 8±2. 6 s versus 12. 4±2. 8 s). Sinusoidal rotation: After sleep deprivation, the gain (0. 55±0. 22) was not significantly different than after a normal sleep night (0. 57±0. 20).
Our study shows that the gain is greater after total sleep deprivation versus normal sleep but only for velocity step and not for sinusoidal rotation. The difference between the two stimulations is the abrupt-onset of the step stimulation compared to the sinusoidal rotation. As it is well-known that such sudden stimulus can automatically grab our attention, we can hypothesized that the unanticipated supranormal gain observed with velocity step is mediated by attentional mechanisms. Interestingly, functional imagery studies have shown sleep deprivation effects on temporo-parietal junction, an area known to be involved both in attention processes and spatial perception.

SP4.9
Binocular asymmetries in the vestibulo-ocular reflex (VOR)
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Previously we found that applying head thrusts to normal subjects at very high accelerations (VHA: 10,000-20,000°/s^2, 300-500°/s, ±20°) generated gaze errors in the vestibulo-ocular reflex (VOR) at magnitudes normally observed in patients with vestibular loss during head thrusts of lower acceleration. Using binocular recordings in this condition, we now observe distinct differences between the two eyes during the first 50ms of this response in normal subjects at VHA.

When either eye was adducting, gaze error increased faster, reaching peak gaze velocities 35. 8±12. 1sec after the head onset, compared to 51. 4±12. 1sec (p<0. 001), when the same eye was abducting. Peak gaze velocity error was a linear function of peak gaze position error. Gaze velocity error of the abducting eye was overall higher than that of the adducting eye. We compared horizontal head fixed saccade dynamics with eye (re: head) dynamics during the VHA head thrust by overlaying all the response trials in terms of disconjugate (eyeright 013 eyeleft) versus conjugate (eyeright + eyeleft) responses. Each subject exhibited his or her own signature pattern of saccade dynamics, while the VOR patterns were similar. Disconjugate versus conjugate velocity plots showed that the abducting eye was initially faster than the adducting eye during both VOR and saccades. The VOR, however, had disconjugacies which peaked at low conjugate velocities (100°/s), while the disconjugacies in saccades peaked at high conjugate velocities (300°/s). In this condition the conjugate accelerations of the VOR are within the same magnitude as that of saccades (±15,000°/s2).

The data suggest that both VOR and saccadic systems exhibit an abduction-adduction asymmetry. While an increased delay due to the presence of an internuclear neuron in the pathway to the medial rectus motorneuron can account for some adduction-abduction asymmetry, there must be other mechanisms to explain the difference in the amplitude of the disconjugacies between the vestibular slow phases and saccades. (Supported by NIH Grant DC00979 and The Clare Boothe Luce Foundation)

SP4.10

Plasticity of the horizontal angular vestibulo-ocular reflex during high-acceleration head rotations
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The vestibuloocular reflex has a remarkable capacity for adaptation following vestibular lesions, in response to spectacle-induced changes in the requirements for compensatory responses, and in response to changes in viewing distance. While the challenges imposed by these conditions differ considerably, specific components of the responses are similar for each situation.

The horizontal VOR in squirrel monkeys following long-term adaptation to spectacles shows changes in gain with respect to the frequency of the rotational stimulus reflecting the low-pass filtered characteristics of the adapta-

tion process. The VOR after 2. 2X magnification has a phase lag that increases with frequency at peak velocity 20 – 150 deg/s. The VOR after 0. 45X miniaturization has a phase lead that increases with frequency. If these dynamics were also indicative of responses to higher velocity rotational stimuli, then retinal slip would be expected to increase with frequency. The reflex would then be ineffective at maintaining stability of images on the fovea for a range of frequencies and velocities for which its function is of critical importance.

Our studies of the horizontal angular VOR evoked by high-frequency, high-acceleration, whole-body rotations in squirrel monkeys have revealed two components to the reflex. These components have been mathematically modeled as linear and nonlinear (phasic) pathways with specific inputs from the vestibular periphery. Parametric changes in the gain of the linear pathway provide an appropriate depiction of the VOR at higher frequencies and low velocities. Responses to rotational stimuli at higher velocities and frequencies provide evidence of a phasic component that, in the squirrel monkey, has a gain that can be modeled with the cube of head velocity. This nonlinear pathway reduces the amount of retinal slip that occurs during head rotations for responses to these stimuli.

This mathematical model of the horizontal VOR can also be used to describe responses in the squirrel monkey after unilateral vestibular lesions (labyrinthectomy and plugging of the three semicircular canals). Following compensation, responses during steps of acceleration in the contralesional direction exhibit the same phasic properties that are seen after spectacle-induced adaptation. Ipsilesional rotations do not exhibit these phasic properties because of inhibitory cutoff.

A similar mathematical model was developed to explain the vergence-mediated changes in gain of the horizontal VOR during rapid head-on-body rotations in humans. We modeled the responses with a linear pathway providing the majority of the input during rotations while viewing a far (1. 24 m) target. Changes in gain induced by viewing a near target (0. 15 m) were modeled by a second phasic pathway adding to the response.

SP4.11

Modeling Contributions of the Linear Vestibulo-ocular Reflex During Off-Vertical Axis Rotation (OVAR)
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OVAR about a head yaw axis induces eye velocity with a yaw bias and modulations in roll, pitch and yaw eye position and velocity as the head reorients relative to gravity. The oscillating components of eye velocity during OVAR were modeled and combined with a model for bias velocity generation to determine how compensatory and

orienting components of the lVOR contribute to the response. The roll and pitch position components had maximum deviations with the side down and nose down head positions respectively and could be modeled by an lVOR orienting mechanism, which was the cross product between a vector along the head yaw and the gravito-inertial acceleration (GIA) vector. The horizontal component had a more complicated relationship to the GIA, having an average phase shift between horizontal beating field position and eye velocity of about 180 deg and could not be modeled with a compensatory lVOR, convergence mechanism or time constant variation in velocity storage due to orientation effects. The phase behavior required the introduction of an orientation mechanism, which depends on the orientation of the naso-occipital axis with the GIA. This mechanism not only directly orients the eyes about a yaw axis, but also modulates eye velocity generated through velocity storage. Thus, "tilt and translation" mechanisms alone are not sufficient to explain the responses to OVAR. It is necessary to have a more generalized orientation system that governs eye orientation in all directions and which also has a modulatory effect on the eye velocity generated by velocity storage. The model also explains the post-rotatory response when subjects are stopped in various positions following OVAR, which orient eye velocity toward the GIA.

SP4.12
Three Dimensional Orienting Eye Movements During Translation While Rotating (TWR) in the Monkey
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Monkeys were sinusoidally translated interaurally or in a naso-occipital direction, at frequency 0.01-0.5Hz while being rotated at a constant angular velocity of 298°/s. This translation while rotating (TWR) produced Coriolis accelerations normal to the direction of linear acceleration as well as centripetal acceleration, which were 90° in phase quadrature, generating a rotating gravito-inertial acceleration field around the head. There are two key differences between this stimulus and off-vertical axis rotation (OVAR). First, TWR generates an elliptically rotating field, while OVAR generates a uniformly revolving GIA. Second, during TWR animals are upright and aligned with gravity, and they are tilted during OVAR, so the dorso-ventral components are different. We studied the three-dimensional response to this stimulus and compared it to OVAR and Slow Static Tilts to determine whether the average direction of gravity was computed in determining the responses to changes in the GIA. We thus questioned whether steady state continuous nystagmus is generated during TWR and whether the orienting and compensatory responses of the lVOR contributed in the same way during TWR as during OVAR. Torsional eye position had a gain of approximately

0.3 over a frequency of translation of 0.01-0.1Hz, at 0.1Hz the position reached to the peak. It then declined linearly to about 0.15 when the frequency went to 0.5Hz. This torsional response was similar to the response do to OVAR at 30° tilt at a rotational velocity that produced the same frequency of linear acceleration. There was also a vertical eye position modulation, which was saccadic when the animal was oscillated in the naso-occipital direction, similar to that obtained during OVAR. In addition, there was a beating field modulation in yaw component as that was found during OVAR. These data suggest that the orienting component of the Linear Vestibulo-Ocular Reflex (lVOR) contributes in the same way to the oscillating horizontal, vertical, and roll eye velocity during TWR as during OVAR. This indicates that the average orientation of the animal, which is aligned with gravity is not an important variable monitored by the central vestibular system during motions that alster the GIA.

SP5.1
Vestibular influences on locomotion: walking versus running
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Prompted by our initial observation that an acute vestibular tone imbalance due to vestibular neuritis causes patients to deviate less from the intended path when running than when slowly walking, we examined healthy subjects when walking or running at different step frequencies during galvanic vestibular stimulation (1 mA for 10 s).

Blindfolded subjects were asked to walk (1 Hz step frequency) or run (3 Hz step frequency) straight ahead toward a previously seen target. The mean gait deviation was 6. 0±2. 4° at 1 Hz and 2. 8±1. 8° at 3 Hz step frequency (n=10; p<0. 001). As walking and running are highly automated processes based on spinal locomotor generators under supraspinal control, we concluded that vestibular input was differentially regulated depending on the locomotion speed and pattern used. Differential effects were also seen when gait deviation was induced by optic flow stimulation using inverting prisms: when walking slowly (about 1 m/s), mean deviation was 0. 22±0. 08 m/s and significantly less when running (about 3 m/s), with mean values of 0. 05±0. 03 m/s (ANOVA, p<0. 01; n=12). In contrast, when a weight (5 kg) was attached to one leg and subjects were asked to walk straight ahead, the thus induced gait deviation did not depend on locomotion speed (n=12).

This argues against the assumption that increased speed generally causes physical stabilization of locomotion. The gait performance of patients with certain pathologies, however, was dependent on locomotion speed: subjective performance and/or measured parameters (lateral deviation, lateral body sway) were improved in patients with central vestibular lesions (6/7 patients with Wallenberg's syndrome) and in patients with cerebellar ataxia (6/6 patients) when running compared to slow walking. On the contrary, patients with spastic hemiparesis (n=8), polyneuropathy (n=12), and Parkinson's disease (n=10) either showed no

difference or became worse with increased locomotion speed.

Conclusion. Vestibular sensory information seems to be more influential when the walking speed is slow; it becomes less important when the speed of locomotion increases. The functional significance of this suppression of afferent and reafferent inflow might be that it reduces potential sensorimotor reactions that would interfere adversely with the optimized locomotion pattern.

SP5.2
Kinematics of head posture during galloping locomotion in Erythrocebus patas
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Kinematic data on head and neck posture were collected for two individuals of Erythrocebus patas. Kinematic measurements were taken from video images and used to assess patterns of intracycle variability in head attitude during quadrupedal galloping. In addition, electromyographic patterns of activation underlying the observed movements were assessed. Two muscles were monitored: semispinalis capitis (biventer cervicis head) and splenius capitis. Both were found to be active in head extension during forelimb support phases. The data reveal a stereotyped pattern of head-neck movements in the sagittal plane during galloping locomotion. Orbital inclination, measured as the angle relative to the gravity vector of the line joining supraorbitale and infraorbitale, was not observed to change significantly during the locomotor cycle, despite large oscillatory movements of the body in the sagittal plane. This suggests that quadrupedal primates stabilize the head and neck in pitch axes during locomotion, possibly to reduce the computational load of the vestibular apparatus in the neural control of head, neck, and eye movements.

SP5.3
Podokinetic stabilisation of body orientation in space on a rotating platform in the dark
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We investigated the extent to which humans provided only with vestibular and podokinesthetic information are able to stabilise their body in a given spatial direction on a rotating platform by stepping counter to the rotation. Previous experiments with passive and active whole body rotations in the dark had suggested that spatial orientation may be significantly influenced by cognitive mechanisms that compensate for the known high pass characteristic of the vestibular apparatus (e. g. , by conscious extrapolation of the initial turning perception). With the present "error-nulling" experiment we sought to eliminate such cognitive interventions and to obtain a more direct access to the vestibular turning sense proper and to its interaction with podokinesthetic cues.

Subjects (Ss; N=14) were placed in upright posture at the centre of a turntable in complete darkness and were instructed to "step in place" whenever there was no platform movement. During platform rotations, they were to actively compensate and keep their body fixed in space by stepping about their vertical axis. Three types of rotation were applied: VC; velocity steps (20°/s or 40°/s) followed by a 120 s period of constant velocity and a sudden stop. VS; five periods of sinusoidal rotation at 0. 012 Hz with 40°/s peak velocity. VN; band limited random noise sequences of 520 s duration.

After the start of VC trials, Ss clearly perceived the platform turning under their feet and were able to compensate the rotation. However, they then gradually reduced their active rotation, stepping in place relative to the platform instead of relative to space; as a result, they were accelerated along an exponential and ultimately acquired the platform velocity. Concomitantly the sensation of platform rotation was lost. Upon platform stopping, Ss would first maintain the spatial velocity they had acquired, and then exponentially decelerate to become stationary. The time constants of these exponential transitions varied considerably among Ss (6 - 76 s) but were similar for the two velocities and for the start and the stop of the rotations. The individual time constants derived from responses to VC also were fairly good predictors of the same subject's stabilisation during VS and VN rotations.

Modelling considerations suggest that stabilisation is not simply the result of a feedback control via the vestibular cue but that perceived platform rotation (constructed from vestibular and podokinesthetic signals) is important.

SP5.4
Fusion of vestibular, optokinetic and podokinesthetic information during rotations towards instructed targets
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In everyday life, orientation in space relies (1) on landmarks and (2) on path integration of signals from vestibular, optokinetic and proprioceptive origin. We here focus on the accuracy of path integration during various combinations of these signals.

12 healthy human subjects (Ss) stood in upright posture at the centre of a turning platform and were exposed to various monomodal, bimodal and trimodal stimulations: V, vestibular; passive body rotation in the dark. O, optokinetic; Julesz pattern rotating about the Ss. P, podokinetic; Ss stepping against platform rotation while in darkness and holding to an earth fixed rail. VO; passive rotation with vision of the stationary pattern. VP, active turning in darkness, platform stationary. VPO; active turning with vision of the stationary pattern. Rotations occurred at one of 3 constant velocities (vC = 15, 30, 60°/s). In all conditions, Ss were to indicate when a (previously instructed) desired angular displacement (DD) ranging from 150° - 900° was reached. DD and vC were randomised. The Ss' performance was characterised by the "targeting gain", defined by GT = actual displacement/DD.

As expected, the trial-to-trial variability of GT depended on the sensory configuration: it was lower in bimodal conditions than in monomodal ones, whereas the trimodal case VPO failed to produce a further improvement. The average of GT increased with turning velocity, being mostly smaller than unity with 15°/s rotations, about unity with 30°/s and exceeding unity with 60°/s (i. e, small velocities are overestimated, large ones underestimated). Noticeably, this velocity dependence was largest in monomodal conditions, intermediate in bimodal, and almost absent in the trimodal condition (VPO). Remarkably also, in condition V, no deterioration of GT was observed that could be attributed to the vestibular time constant.

We hypothesise that path integration is based on an internal representation of turning velocity that is a weighted average of (1) the contributing sensory cues and of (2) an internally stored "default" velocity. Conceivably, the default velocity (which in our experiments corresponded to the mid-range of the occurring turning velocities) is determined by cognitive factors such as previous experience and expectations. Its relative weight would decrease as more sensory cues become available; hence its small effect in the trimodal case and the large under (over)estimations of fast (slow) rotations during monomodal stimulation. This view is confirmed by experiments showing that deliberately impoverishing sensory information augments the latter effect

SP5.5

The importance of vestibular information for postural control depends on velocity of surface tilt

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Vestibular information is known to be important for postural stability on tilting surfaces. The relative contribution of vestibular, somatosensory, and visual information to postural control when the surface tilts at different velocities is unknown.

We investigated how tilt velocity influences postural orientation and stability in 9 subjects with bilateral vestibular loss and 9 age-matched healthy subjects. Subjects stood on a force platform that tilted 6 degrees toes-up under varied velocity conditions (0. 25-32 deg/s) with and without vision. Postural responses were analyzed using kinematic, ground reaction force, and trunk and leg EMG data.

Subjects with vestibular loss were significantly more unstable than controls during surface tilts with eyes closed, but not with eyes open. Visual information effectively compensated for lack of vestibular information across a wide range of tilt velocities. With eyes closed, vestibular loss subjects were most unstable within a narrow range of tilt velocities (2-8 deg/s), losing balance in over 90% of trials under the 4 deg/s condition. Subjects did not fall during slow tilts (0. 25-1 deg/s) and fell only rarely during fast tilts (16-32 deg/s). During slow-to-medium velocity

toes-up surface tilts, vestibular loss subjects leaned further backward than controls, as if trying to maintain body orientation with respect to the surface rather than to gravity. The initial, passive biomechanical response to surface tilts changed as velocity increased. Faster tilts resulted in forward, rather than backward, initial trunk pitch, providing a different combination of sensory inputs and requiring a different direction of postural response. Comparison of relative timing between trunk and ankle angles and EMG activity suggests that backward leans and falls were not caused by absence of a vestibulo-spinal reflex, but instead resulted from an active postural correction based on a misinterpretation that the body had tilted over a stable surface.

This study suggests that vestibular information contributes to interpretation of somatosensory inputs from the feet for stance control on unstable surfaces when vision is not available. Vestibular information is critical for stability during surface tilts with velocities around 4 deg/s, which are too fast for responses that depend on the slower graviceptor somatosensory system and too slow for fast somatosensory-triggered responses or passive stabilization from trunk inertia. (Support: NIDCD #DC01849 & Foundation for Physical Therapy.)

SP5.6

Habituation to galvanic vestibular stimulation depends on sensory reweighting

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We previously observed that subjects standing with eyes closed on a tilting support surface (SS) orient to the SS for small tilt amplitudes suggesting that subjects rely primarily on proprioceptive orientation cues in these conditions. However, as SS tilt amplitude increases, subjects orient more to earth vertical. This changing behavior may be explained by a reweighting of sensory orientation cues whereby the postural control system increases its reliance on vestibular cues as SS amplitude increases. If this explanation is correct, we predict that body sway evoked by galvanic vestibular stimulation (GVS) should increase with increasing SS tilt amplitude. Furthermore, if the well known habituation effect to repeated GVS is due to a central mechanism associated with sensory reweighting, we predict that habituation will decrease with increasing SS tilt as subjects rely more on vestibular information for balance control.

To test our predictions, medial-lateral (M/L) body sway was measured while subjects stood with eyes closed on a SS that tilted in a M/L direction. Test conditions included fixed SS (0 deg tilt), tilts according to a pseudorandom profile at 4 different amplitudes (1 deg , 2 deg , 4 deg , or 8 deg), and sway-referenced SS. In each condition, a 0. 75mA pulsed bilateral, bipolar GVS was delivered through electrodes on the mastoid processes. Each test lasted about 300s, during which 6 cycles of the pseudorandom SS, 24 positive and 24 negative GVS pulses were presented. Since

the pseudorandom SS stimulus was mathematically uncorrelated with the GVS stimulus, the body sway responses to the SS tilt could be analyzed separately from the GVS, and then subtracted leaving only the response to the GVS. The peak body sway amplitude in response to each GVS pulse was measured. The mean peak response provided a measure related to the vestibular contribution to postural control in each condition. The habituation to GVS was characterized by a habituation index equal to $100(Pi-Pf)/Pi$, where Pi and Pf are the mean peak response in the first third and the last third of the trial, respectively.

Results showed an increasing body sway response to the GVS with increasing SS tilt amplitude. Additionally, the smallest GVS response was obtained in the fixed SS condition and the largest response in the sway-referenced SS condition. This result supports our prediction that the vestibular contribution to postural control increases with increasing SS motion. The galvanic habituation index was greatest (about 55%) in the fixed surface condition, decreased with increasing SS motion amplitude, and was lowest (about 5%) in the sway-referenced SS condition. The amount of habituation of the galvanic response was inversely correlated with the relative sensitivity to vestibular stimulation. This result supports the hypothesis that habituation of the vestibulospinal response to galvanic stimulation is a centrally mediated phenomenon associated with the sensory reweighting process. (Supported by grants NIH AG17960, DC01849, and Research Exchange Studentship from University of Bologna, Italy.)

SP5.7

Time delay compensation mechanisms in the human postural control system
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It is generally assumed that the human postural control system uses active regulation via feedback mechanisms to maintain quiet upright stance. This regulation necessarily involves a time delay due to sensory transduction, neural transmission, central processing, and muscle activation. Since time delay is destabilizing to a feedback control system, we wanted to determine if neural mechanisms exist that compensate for time delay. Two possibilities were considered. First, vestibular sensory cues might contribute to postural control with shorter time delays than proprioceptive cues. In this case, the time delay should decrease in situations where subjects rely more heavily on vestibular information for balance control. Second, neural "predictive" mechanisms might exist that compensate for time delay. In this case, the actual time delay would remain constant for all test conditions, but the predictive compensation would change the dynamic behavior of the postural control system at higher frequencies.

Postural dynamic behavior of normal subjects was quantified in experiments that measured sagittal plane body center of mass (COM) rotation in response to support surface (SS) rotational tilts (eyes closed to eliminate visual cues). Transfer function gain and phase measures relating the COM response to the SS stimulus were calculated using spectral techniques. Phase functions showed increasing phase lag with increasing stimulus frequency consistent with the existence of a time delay. The gain and phase functions varied with stimulus amplitude showing overall decreasing gain and less high frequency phase lag with increasing stimulus amplitude. This result is potentially consistent with an increasing contribution of shorter latency vestibular information. However, reanalyzing the data using time domain techniques to estimate impulse response functions showed that the time delay had a fixed value of about 150 ms independent of stimulus amplitude. This finding eliminates the possibility that shorter latency vestibular cues contribute to time delay compensation.

An alternative explanation is that neural "predictive" mechanisms compensate for time delay. The inclusion of a "Smith Predictor" into a simple feedback model of postural control produced results compatible with experimental findings that showed reduced high frequency phase lags at higher SS stimulus amplitudes. However, it was not necessary to include a predictive mechanism to explain responses to lower amplitude SS stimuli, suggesting that predictive compensation is only utilized in more challenging conditions. (Supported by NIH AG17960)

SP5.8

Rotations in a vertebrate setting: group theoretic analysis of vestibulocollic projections
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Rotational movements of the head are registered by the semicircular canals of the vestibular system. Physically, the movements are unified in the sense that rotations about different axes happen to the same body. However, the different degrees of freedom are separately sensed by the receptors on both sides, with approximate symmetry. They are re-integrated in the central reflex pathways and in behavior, but the re-integration is incomplete, as evidenced by motion sickness, illusions, and cue-free perceptions. The biological problem that motivates this study is the fragmentation and re integration of sensorimotor space.

As a first step to understanding this fragmentation, this study analyzes a sensorimotor structure that includes all three rotational degrees of freedom, along with motor apparatus that reflects the right-left, front-back, and up-down directions of the vertebrate body. We use group theory to analyze the reported results from the literature on vestibulocollic projections to neck motoneurons. The sensorimotor three-dimensionality of rotation is maintained over the range of head positions for small head motions, providing local sensorimotor symmetry. In addition, head and trunk position modulates vestibulo spinal responses, indicating that some global sensorimotor spatial symmetry exists.

Our group theoretic analysis of the vestibulocollic projections confirms that the organizational structure has the rec-

tangular symmetry suggested by the vertebrate body, along with the rotational symmetries suggested by the semicircular canals. The reflection and rotation operators maintain the three sensorimotor rotational degrees of freedom for head/neck movements.

There are eight innervation patterns on neck motoneurons: right and left flexor and extensor, and right and left side muscles of two types, which we call "directed" and "alternating". These eight innervation patterns are the complete set of possible combinations of inhibitory/excitatory polarities from three canal pairs.

Our group theoretic analysis indicates that these eight innervation patterns are organized as the vertices of a cube. The two types of side muscles provide the vertical direction. As the head rotates in physical space, the cube rotates in sensorimotor space.

The organizational structure found among canal projections must either be extended by otolith projections and proprioceptive afferents or form an overlapping organization. Further research is required to determine whether the sensorimotor spatial structure of the vestibulocollic projections is widespread in nervous systems or whether there are several complete structures that are fragmented and reintegrated.

SP5.9

Neck but not mastoid vibration causes short latency emg activation of lower leg postural muscles

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Background. Cervical input is considered to be of importance to the postural control. We wanted to study how fast cervical proprioceptive information induced muscular responses in the lower leg to control posture in the standing human. We investigated lower leg muscle EMG and force plate data from 10 healthy normal subjects, when perturbed by posterior neck muscle vibration.

Material and Methods. 10 healthy volunteers were investigated with vibration applied to cervical muscles when standing on a force plate. EMG were recorded from Tibialis, gastrocnemius and soleus on both legs.

Results. At onset of vibration the tibialis anterior was activated at latencies of 70-100 ms while the triceps surae was inhibited at the same latencies. At offset the opposite pattern was observed. When applying vibration to the mastoid in an extended series of subjects no similar responses were observed.

Conclusions. These findings suggest that a short latency integrative system, rather than a direct reflex, mediates the cervical influence on posture. The short latencies also imply that activation of postural muscles in response to vibration toward the neck muscles occur faster than would have been expected if they only were caused by a perceptive illusion of movement.

SP5.10

The influence of head position on postural sway during galvanic vestibular stimulation

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The purpose of this study was to determine the relationship between yaw head-on-trunk position and the direction of postural sway in response to sinusoidal galvanic vestibular stimulation in healthy adults.

Methods. Thirty healthy adults aged 21- 65 years (mean 41. 3 ± 10. 9, 15 M, 15 F) having no history of neurologic or otologic dysfunction, no history of neck, spine or lower extremity injury, and normal vestibular function testing, participated in the study. Sinusoidal binaural, bipolar galvanic vestibular stimulation (GVS) was applied over the mastoids with a peak current intensity of 0. 5mA and a frequency of 0. 25 Hz. Each of the two test sessions consisted of six 30-second trials for each of 7 head-on-trunk yaw positions (0, ± 15º, ± 30º, ± 45º): 3 with GVS and 3 without GVS. Anterior-posterior (AP) and medial-lateral (ML) head position, and center of pressure (COP) were recorded continuously during each trial. Subjects completed two sessions 2-10 days apart to assess test-retest repeatability.

Data Analysis. Head and COP AP and ML recordings were bandpass filtered at the stimulus frequency, and the 30-second trial was divided into 7. 5 cycles based on the stimulus. For each cycle, the resulting transverse plane scatter plot was fit with an ellipse, which provided parameters of major and minor axis length and direction of sway. The median angle of the direction of sway and the mean yaw head-on-trunk position was calculated for each trial. The direction of sway of the COP and head were regressed on mean yaw head-on-trunk position. The slope and intercept of the line of best fit for each subject and session was calculated.

Results. Significant differences in the parameters of the ellipse were found between stimulation and no stimulation trials. Without GVS, no relationship was found between the yaw head position and the sway direction. With GVS, a linear relationship was found between the yaw head-on-trunk position and both the COP and head sway direction. The mean slope was 1. 15 ± 0. 30. Significant differences were not found between sessions using paired t-tests.

Conclusions. Cervical somatosensory information interacts with galvanic vestibular stimulation in such a way that the direction of postural sway is oriented along the interaural axis of the head rather than along the AP or ML axis of the trunk.

SP5.11

Ankle and hip joint kinematics affect neck muscle activation during whole-body rotation

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The peripheral vestibular apparatus provides informa-

tion about head acceleration in an inertial frame. The central vestibular nuclei, however, also generate an estimate of body velocity and orientation required for postural control. Arthrokinetic and stepping-around nystagmus provides evidence for limb somatosensory signals and/or motor commands being capable of driving compensatory ocular motor responses to body motion, even with the head at inertial rest (Brandt, Bles). Recent investigations of the podokinetic effect (Gordon, Weber) demonstrate a more dynamic remodeling of the central vestibular mechanism by motor activity in the lower extremities. Sensor fusion (Mergner) provides a framework for combining vestibular and somatosensory information to maintain haptic and inertial cues in register. In order to investigate this interaction, we studied how well standing subjects could keep their body moving *en bloc* while standing on a support surface which rotated about the vertical axis.

Normal human subjects stood on a rotating support surface driven by a sum of sines stimulus, with frequency content between .05 and 2.8 Hz. Head, pelvis, leg and foot angular velocities were recorded while patients were instructed to hold their body such that that the head, trunk and legs all rotated together with the support surface. Bode plots were obtained for each segment relative to the platform (input). Equations of motion relate each body segments' angular acceleration, velocity and position to torques acting on the segment. Each joint has both zero order (K, spring stiffness) and first order (B, viscous damping) properties. Control laws were postulated which incorporated feedback terms through which rotation at a joint not adjacent to a given segment could nevertheless influence the torque acting on that segment (e.g. effect of hip rotation on neck motion, $\gamma_{neck-hip}$).

At frequencies below ~1 Hz, all body segments had nearly unity gain, indicating success in performing the en bloc task. At higher frequencies, pelvis velocity was attenuated relative to the feet (low pass filter), however head gain was significantly higher.

Models were fit which included all possible γ's, no γ's or selected combinations. The best fits were found for models which incorporated $\gamma_{neck-hip}$ and/or $\gamma_{neck-ankle}$. Other models with more parameters, but which did not include either of these terms, were always poorer fits. Some individuals' fits were improved when $\gamma_{hip-ankle}$ was included.

In a "passive" implementation of *en bloc* behavior, joint impedances would be set by tonus or modulation of stretch receptor gain to resist any perturbation. The control law in this case would be simply to command all joint velocities to zero. In such a system, the best a segment could do is to match the angular velocity of the segment immediately below. In our observations, the head was able to match foot velocity much better than the trunk, indicating an "active" process providing a motor command to neck muscles based upon hip and ankle rotation (error signal). The up-channeling of information between the feet and the head allows for a binding of the inertial (vestibular) frame to the material environment.

SP6.1
The role of visual and vestibular cues in determining perceptual stability during head movement
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The perceptual world remains stable during voluntary rotational and translational head movements. How do the vestibular and visual sensory systems contribute to this sensation of stability? Translation and rotation components of self motion are detected by different patterns of optic flow and by different divisions of the vestibular system. A given movement can also involve different sensors depending on the orientation of the movement with respect to gravity. For example yaw rotation while sitting upright does not involve a change in orientation relative to gravity but does when supine. Similarly translation along the dorsal-lateral axis of the head add and subtract from gravity when standing up but not when supine. To measure the overall response to movement we exploited the fact that during a voluntary head movement the perceptual world normally remains stable. To achieve this requires knowing about the movement, especially about the movement of the eyes in space; predicting the expected visual movement of the world and comparing the actual and expected movements. We measured how much the visual world could be moved during head rotations and translations around various axes and still be perceived as visually stable. We looked for differences in performance that might correspond to the different sensors involved in a given movement.

Our subjects' task was to distinguish self produced visual motion from external visual motion during rotation around the yaw, pitch and roll axes and during translation in the naso-occipital, inter-aural and dorsal-ventral directions. The axis or direction of motion was arranged to be parallel or orthogonal to the direction of gravity. Subjects wore a head-mounted display (HMD). The HMD was updated in response to head movement which was monitored by a mechanical tracker. The ratio between head and image motion was varied. Subjects indicated whether the display appeared earth-stationary (perceptually stable) or appeared to move relative to the ground.

For both rotation and translation there was a large range of ratios of visual motion to head motion that was tolerated as perceptually stable. The ratio most likely to be accepted as stable corresponded to visual motion faster than head motion. For rotation there were no consistent differences between yaw, pitch or roll axes and the orientation of the axis relative to gravity also had no effect. For translation, motion in the naso-occipital direction was on average matched with less visual motion than inter-aural or dorsal-ventral motion.

SP6.2
The subjective visual horizontal and vertical in 65 patients after vestibular deafferentation
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In peripheral vestibular lesions, the deviation of the subjective visual vertical (SVV) and subjective visual horizontal (SVH) is due to a tonic offset of torsional eye position and as such an indirect measurement of utricular function. We measured the SVV and the SVH in 65 consecutive patients before and 6 months after translabyrinthine surgery for vestibular schwannoma.

Method: Tumor size was measured with MRI and electronystagmography was performed including bithermal caloric tests, spontaneous and headshake nystagmus. The subjective visual horizontal and subjective visual vertical (SVH-V) was measured 4 times each and the mean was calculated. The patients were examined approximately 3 months before and 6 months after surgery.

Results: The mean SVH-V was 1.6 degrees before surgery and increased to 5.0 degrees after surgery (p<0.001) toward the ipsilesional side. The individual variation was great and SVH-V ranged from 0.8 to 13.4 before surgery and 0.9 to 16.4 degrees postoperatively. Patient age, tumor size, the degree of pre-operative canal paresis or the presence of spontaneous or head-shaking nystagmus could not explain this variance. With linear regression analysis only 20.3% of the SVH-V increase after surgery was explained by the SVH-V before surgery. 12.5% of the variance of the SVH-V before surgery was explained by the age of the patient. This might suggest an age-dependent delayed central compensation or perceptive changes or simply that the older patients had a difficult time understanding the instructions for the SVH-V test.

Conclusion: We propose that there is an idiosyncrasy of the SVH-V compensation after unilateral vestibular de-afferentation and that it is not related to the general course of adaptation. This might be of importance for the chronic balance disturbances that some of these patients experience.

SP6.3

Translation perception and its relationship to reflex eye movements
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Otolith-mediated vestibular responses such as the linear vestibulo-ocular reflex (LVOR) are highly frequency-dependent. The LVOR becomes increasingly robust as motion frequency increases (i. e. high-pass dynamics, >0. 5Hz). In this study, we examined the relationship between the dynamics of interaural translation perception and corresponding reflex eye movements. In order to assess the contribution of otolith information in translation perception, we utilized frequencies that span the physiological range of the system (i. e. 0. 1-2. 0 Hz). Previous perception studies have been mostly limited to modest frequencies (<0. 5Hz), due in part to the difficulty of assessing perception during high frequency motion. We overcame this issue by using a novel manual image stabilization task (parametric adjustment task) in conjunction with a more traditional method (joystick task). The translational LVOR was also assessed in a subset of subjects in order to compare the dynamics of perception and reflex responses.

During the "joystick task", subjects were translated sinusoidally on a servo-controlled linear sled in darkness. Subjects used a joystick to control the position of a laser target in order to maintain an earth-stationary perception on a screen at 1. 4m distance. During the "parametric adjustment task", target position was controlled by a sinusoidal signal at the same frequency as translation. Subjects independently adjusted the magnitude and phase of the control signal with two potentiometers until the target appeared to be earth-fixed. There was good concordance of results between the two tasks. However, the joystick task was difficult to accurately perform $\geq 0. 5$Hz, while parametric adjustment task proved difficult <0. 5Hz.

Translation perception demonstrated high-pass characteristics; mean gain was 0. 92 at 2. 0Hz, declining to 0. 70 at 0. 1Hz. Phase at 2. 0Hz was near 0º, but a phase lead developed as frequency declined, reaching 12° at 0. 1Hz. A separate experiment (NASA-AMES) on an air-bearing sled (reducing non-otolith cues) showed a more profound attenuation of perception performance at low frequencies (i. e. decreased gain and increased phase lead). LVOR dynamics followed that of perception, but depended upon the context of imagined earth or head fixed targets. These results suggest that translation perception, like the LVOR, is influenced by both otolith and non-otolith cues. Otolith information predominates responses at higher frequencies (>0. 5Hz), while non-otolith cues are most influential at lower frequencies ($\leq 0. 5$Hz). (Supported by the following grants: NIH DC04153, NIH DC01935, NEI EY01319)

SP6.4

Influences of vestibular and non-vestibular cues in the estimation of the subjective vertical
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It is well known that the perception of verticality does not only depend on visual cues but is affected by head orientation relative to gravity and/or linear acceleration of the head and body. Although the influence of vestibular signals has been studied extensively, little is known about the underlying mechanisms that may lead to systematic deviations of the perceived verticality with respect to gravity.

Here, we have used three different paradigms to test the ability of subjects to estimate the subjective visual vertical. The aim was to investigate the hypothesis that activation of both the semicircular canals and otoliths provides an optimal vestibular input to compute changes in self-orientation in space. A second goal was to investigate Mittelstaedt's theory (1983) of idiotropic vector. We have studied in 7 -19 subjects: (a) the setting of a luminous line according to the perceived visual vertical in darkness, (b) the ability to estimate the direction of earth vertical by performing saccades, and (c) the ability to verbally estimate body position. Subjects were rapidly tilted (180°/s2) on a human turntable from upright to different roll positions

ranging from 90° left to 90° right side-down.

Our results show no significant time evolution when testing the paradigms immediately (semicircular canal signals present), 25 s and 90 s (little or no semicircular canal information) after the tilt. In applying Mittelstaedt's theory, we found that our results cannot be described in terms of a head-fixed, time-invariant idiotropic vector. (Supported by the SNF #31-57086. 99 and the Betty & David Koetser Foundation for Brain Research.)

SP6.5
The effect of head position on illusory self-motion in artificial gravity
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The effects of cross-coupled stimuli on the semicircular canals are influenced by the subject's head position with respect to gravity but not by the subject's head position relative to the trunk. Seventeen healthy subjects made out of plane head yaw movements while lying on a horizontal platform (MIT short radius centrifuge) rotating at 23 rpm. The subjects reported the magnitude and duration of the illusory pitch or roll sensations elicited by the cross-coupled rotational stimuli acting on the semicircular canals. The results suggest an influence of head position relative to gravity. The magnitude estimation is higher and the sensation decays more slowly when the head's final position is toward nose-up (gravity in the subject's head x-z-plane) compared to when the head is turned toward the side (gravity in the subject's head y-z-plane). The results will be discussed with respect to artificial gravity in space and the possible role of pre-adaptation to cross-coupled angular accelerations on earth.

SP7.1
Human eye-movement responses to galvanic vestibular stimulation are linear, symmetrical and additive
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Recent studies have shown that, although responses to long-duration, constant-current surface galvanic vestibular stimulation (GVS) show substantial inter-individual variability, individual subjects show a reliable, repeatable, idiosyncratic oculomotor response pattern. The aim of the present study was to examine the metrics of 3-D eye-movement responses to maintained (120 s), unilateral and bilateral surface GVS. Eye movements were measured using computerised video-oculography.

Two experiments were conducted: Experiment 1 examined whether the relationship between current strength and the magnitude of the normal eye-movement responses is linear; and Experiment 2 examined A) whether the normal response to surface GVS is symmetrical when comparing sides, B) whether the normal response to surface GVS is symmetrical when comparing stimulus polarities and C) whether there is simple additivity of the response from each side to unilateral and bilateral stimuli. 5 subjects partici-

pated in Experiment 1 and 8 subjects participated in Experiment 2.

In both experiments, the onset of stimulation produced characteristic eye-movement responses: changes in torsional position with the upper pole of both eyes rolling towards the anode and away from the cathode; together with horizontal and torsional nystagmus with slow phases towards the anode and away from the cathode in darkness; and negligible vertical nystagmus. These responses reversed direction at stimulus offset. In the fixation condition of Experiment 1, the magnitude of ocular torsional position (OTP) and torsional slow phase velocity (SPV) responses showed a linear relationship over conditions of increasing current strength, as did OTP, torsional and horizontal nystagmus responses in darkness; thus, there is no evidence of different thresholds for velocity and position responses. The results of Experiment 2 showed that responses to unilateral stimulation are symmetrical between stimulated sides, symmetrical between stimulating polarities, and additive (with respect to responses to bilateral stimulation).

Our findings of symmetry between stimulating polarities, or of excitation and inhibition, do not contradict the asymmetries found in response to stimuli of much larger effective magnitudes, whose ability to modulate firing rates are affected by the limit at zero spikes/s. Our results also provide factual evidence for the assumption that in the human there is almost exact linear addition from the two sides of both canal and also otolith input. The principles derived from these findings, as well as those of recent studies, provide a foundation for our work investigating eye-movement responses to surface GVS in patients with known types of vestibular dysfunction.

SP7.2
Predicting superior colliculus spike trains for strongly perturbed saccades
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We have recently shown that blink-perturbed saccades have strongly curved and highly variable 2D trajectories, markedly reduced peak velocities, and increased movement durations (by 200-300%). Despite these prominent effects, the endpoint accuracy of the perturbed saccades remains unaffected when compared to normal control saccades. Recordings from saccade-related burst neurons (SRBNs) in the deep layers of the Superior Colliculus (SC) during this paradigm show that, despite a strong reduction of a cell's mean and peak firing rate, and a marked increase of burst duration, the number of saccade-related spikes remains virtually unaffected.

A detailed analysis of the spike trains shows that the stereotyped relation for control saccades between instantaneous firing rate and current motor error does not hold for perturbed saccades. However, when the cumulative number of spikes, C(t), is plotted against the instantaneous (delayed) displacement of the eye along the saccade displacement vector, D(t-20ms), the resulting response curves are identical for both perturbed and control responses. This

finding holds for all (optimal and non-optimal) saccades with their displacement vectors into the cell's movement field.

We hypothesize that SRBNs emit a feedforward dynamic signal to the brainstem that encodes a straight displacement of the eyes. On the basis of a quantitative movement field description that relates the total number of spikes in the burst of an SRBN with the total saccade displacement vector, we predicted the detailed spike trains for each saccade into the movement field. Interestingly, this simple model is applicable to both control and to highly perturbed and curved eye movement responses.

SP7.3
Demodulation techniques for the analysis of eye movements
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Eye movements produced by vestibular mechanisms often exhibit modulation by a variety of factors (e. g. , viewing distance, ocular eccentricity). Typical analyses of vestibular responses to sinusoidal stimuli are carried out in a fashion that can highlight such modulatory influences, but do not clearly discern temporal relationships between modulatory factors and harmonic responses. We present a straightforward application of the Hilbert Transform (HT), a tool often used for envelope recovery of amplitude-modulated signals, that allows for convenient analysis of such relationships. We have implemented an initial application of this technique through simulation, and have extended the analysis to include temporal relationships between vergence and response amplitude of the linear vestibular ocular reflex (LVOR) during sinusoidal interaural motion in squirrel monkeys.

Simulated data consisted of sinusoids (0. 25-4Hz) modulated by four different signals: unmodulated, rectangular pulse (5-sec), triangular pulse (5-sec), and slowly varying (0. 5Hz sinusoid). Real data consisted of squirrel monkey eye movements in response to 4Hz linear oscillation. The HT was applied to both data types to recover the modulating envelope and in turn response amplitude. Response phase was recovered by subtracting the phase recovered by the HT of the modulated response from that computed by the HT of the stimulus. For comparison with earlier methods, response parameters were also calculated on a cycle-by-cycle basis using spectral techniques, while HT-calculated parameters were averaged by cycle stimulus as well.

Parameters calculated from 4Hz simulated data showed excellent concordance between the HT and the spectral method, independent of the waveform shape. Modulatory waveforms with discontinuities (rectangular) produced more high frequency ripples on HT-derived response amplitude and phase. For modulation with a low-frequency sinusoid, the HT was robust as long as stimulus frequency was greater than the modulation frequency. For actual eye movement data, sensitivity and phase recovered

by the HT agreed well with spectral-based counterparts. Correlation analysis between continuous response amplitude recovered from the HT and actual vergence showed that the change in LVOR amplitude preceded change in vergence by roughly 40-msec.

The Hilbert Transform is a practical technique well suited for tracking time-sensitive changes in eye movements invoked by harmonic stimuli. It permits robust analysis of modulatory influences on LVOR and a time resolution that is limited only by sampling rate. It is applicable to vestibulo-ocular responses to stimuli within usable frequency ranges and can be naturally extended to other classes of eye movements.

SP7.4
Meniere's disease patients have abnormalities of vergence
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Purpose: To investigate whether prism glasses can be useful in therapy against vertigo of Meniere's type.

Method: Unilateral Meniere's disease patients were prescribed spectacles with addition of prisms according to the guidelines described by G. P. Utermohlen in 1941. The effect of treatment was rated by the patients themselves in response to a written request. Also a vergence difference was measured. The difference in heterophoria between far and near , was quantified by subtracting the prismatic correction needed in a Maddox-rod test at fixation distances of 0. 4 m from that at 5 m, such that this difference is positive in esophoria and negative in exophoria

Results: In the preliminary results a total of 92. 7% of all patients scored 2 or higher, thus reporting an improvement on vertigo . A highly significant main effect of vergence difference was observed (p < 0. 00003): the larger the difference, the greater the average success of therapy. Of the 36% with a vergence difference greater than 3 prism diopters, 96. 2% reported an improvement. The greatest success rate was reached in the ipsilateral group with patients whose vergence difference was greater than 3 prism diopters.

Conclusion: Prism glasses alleviate vertigo in Meniere's diseases. It has, however, not yet been established that Meniere's disease patients have abnormalities of vergence. This non-invasive, non-pharmacological therapy for vertigo is worthy of further exploration

SP7.5
Dynamic Bielschowsky head-tilt test
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A positive Bielschowsky head-tilt test (BHT) is the cardinal finding for diagnosing unilateral trochlear nerve

palsy (uTNP): Tilting the head towards the paretic eye leads to an increase of vertical-torsional deviation between the two eyes. In clinical use, this test is performed in a static fashion, comparing the vertical deviation upon head tilt to both sides. To determine the instantaneous ocular rotation axes in patients with uTNP, we applied BHT in a dynamic fashion. 11 Patients with uTNP and 11 healthy subjects were asked to monocularly fix upon targets on a Hess screen, while they were rotated about the roll axis on a motorized turntable (0. 3 Hz). 3D eye movements were recorded with dual search coils. Under viewing condition, the rotation axis of both the healthy and the paretic eye of patients with uTNP was close to the line of sight. The rotation axis of the covered fellow eye, however, followed gaze direction as well, but systematically deviated towards the nose relative to the line of sight (covered palsied eye: 16. 9 ± 5. 8 SD, covered healthy eye: 17. 0 ± 6. 9 SD, values for gaze straight ahead). Rotation axes remained stable during head roll.

The nasal deviation of the rotation axes can be explained by the absent contribution of the superior oblique muscle to ocular counterrolling, if the palsied eye is covered, and an overaction of the contralateral inferior rectus muscle (yoke muscle), if the healthy eye is covered. This phenomenon represents a kinematical consequence of Hering's law. In conclusion, in patients with uTNP, the vertical-horizontal trajectories of the covered eye on the Hess screen during dynamic BHT are a direct consequence of the nasal deviation of the ocular rotation axes from the line of sight. - Supported by Swiss National Science Foundation (32-51938. 97 / 31-63465. 00) and Koetser Foundation for Brain Research (Zurich, Switzerland).

SP7.6
3D coordinates of visually guided saccades and smooth pursuit eye movements depend on gravity
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Visually guided saccades and smooth pursuit eye movements during which animals redirect gaze while maintaining an upright orientation have been previously shown to conform to a particular 3D strategy, known as Listing's law. When the head is passively tilted relative to gravity, the orientation of the displacement plane for visually guided saccades changes in the direction opposite to the tilt with approximately 10% gain. To understand the origin of these gravity-dependent effects, we further studied visually guided saccades and smooth pursuit eye movements in a structured visual environment that was tilted (either statically or dynamically) relative to gravity. Specifically, two rhesus monkeys were trained either to fixate targets LED's or to track with smooth eye movements a laser spot that was projected onto the inner wall of a light tight sphere that surrounded the animal completely. The laser target moved with 0.1Hz ± 15° at different horizontal and vertical eccentricities relative to straight ahead (±10°, ±15°, ±20°). In the static condition, the monkey and its visual surround were

either upright or tilted through 30° or 90° in various orientations relative to earth vertical (nose up/down, ear up/down). In the dynamic condition, the monkey as well as the visual surround were rotated in synchrony at speeds of 60°/s or 180°/s. We report that 3D eye position during pursuit and saccades was maintained in displacement planes that did not remain fixed to the head, but systematically shifted opposite to the change in head orientation relative to space. Thus, the 3D spatial coordinates of not only saccades but also smooth pursuit eye movements are defined according to static and dynamic otolith cues signaling head orientation in space. We suggest that oculomotor signals are transformed into gravity-dependent coordinates at the level of the velocity-to-position integrator in the brain stem. Supported by the SNF 31-57086.99, the Betty & David Koetser Foundation, EY12814 and NAG2-1493.

SP8.1
Modelling predictive processes of gaze control during head-fixed and head-free pursuit
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When human subjects track the continuous movement of a visual target with the head free or fixed, there is strong evidence of prediction in the relatively small phase errors generated at frequencies above 1Hz. The predictive processing acts very rapidly and experimental evidence that we have obtained suggests that this is accomplished through the short-term storage of pre-motor drive information and its subsequent release under the control of separate timing mechanisms. In its simplest form the short-term store holds information about a single target velocity and the replay of the store at an appropriate time leads to the generation of anticipatory smooth pursuit movements.

However, in recent experiments it has been shown that complex sequences containing at least four speeds and two directions of motion can also be learned very rapidly after a single viewing of the motion sequence. Analysis of these multi-ramp sequences suggests that such complex patterns of smooth pursuit may be obtained through the concatenation of pre-programmed anticipatory responses to individual components of the sequence.

This evidence has been used to build a dynamic model that applies both to the head-fixed control of ocular pursuit and to suppression of the vestibulo-ocular reflex (VOR) during head-free pursuit. The basis of the model is that, in addition to the visual velocity error feedback pathway, there is an internal re-afferent feedback pathway that holds velocity drive information in a temporary store. A separate mechanism is responsible for estimating the time at which to release the store, based on stimulus periodicity or other external timing cues that may be present. The main feature of this model is that it not only accounts for the reduction in phase error observed during the tracking of periodic stimuli, but also simulates the slow-onset anticipatory movements that can be observed prior to target onset during repeated target motion presentation.

In head-free pursuit conditions, where the same prin-

cipal is applied to both head and gaze control, the model simulates the predictive changes in VOR suppression as well as the dynamic characteristics of the head movement itself. But perhaps most importantly, the model effectively simulates how short-term memory processes may be used to allow predictive pursuit of complex patterns of target motion. It indicates how such tracking behaviour can be rapidly acquired, thus facilitating the ability to track moving objects in everyday conditions where patterns of movement are frequently encountered but frequently change from moment to moment.

SP8.2
A physiologically-based computational model of horizontal vestibular nystagmus using genesis
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The modelling program GENESIS was used to model the network of projections of vestibular, excitatory and inhibitory burst neurons (EBNs and IBNs) and pause neurons (PNs) in and around the vestibular and abducens nuclei(Curthoys 2002, 143: 397-405) to see if the known neural connections can actually work to produce the slow and quick phase of vestibular nystagmus. The neurons in this network are based on known anatomy and physiology in the cat, mainly from the work by Shimazu and his students, and they were modelled by multicompartmental Hodgkin-Huxley-style spiking neurons using real values or reasonable values for some of the unknown membrane parameters. This model produced spike output from the modelled abducens neurons corresponding to the spike output of real abducens neurons during the slow and quick phase of vestibular nystagmus.

There was a close correspondence between the output of the model and the characteristics of real quick phases (timing, peak velocity, duration etc) in guinea pigs during the nystagmus produced by sinusoidal angular acceleration before and after unilateral vestibular loss. The strength of this model is that it ties known anatomy and physiology together using neural modelling programs to actually generate the complex behavioural pattern of the slow and quick phases of vestibular nystagmus. Obviously many other neural connections remain to be established but the very simple realistic model here performs surprisingly well and provides an easy opportunity for the addition of refinements and enhancements and other neural inputs.
The model has highlighted the need for better experimental data on the quick phase in vestibular nystagmus, both in guinea pigs and humans. The quick phase is usually removed (by "de-saccading") during data analysis but we consider that such a process may be eliminating potentially valuable information about vestibular function.

SP8.3
A linear, steady state model of canal-otolith interaction in the VOR predicts ambulation performance
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A model of the VOR derived for whole body yaw rotation about centered and eccentric axes was applied to data collected during treadmill ambulation and dynamic posturography. The model incorporates linear summation of otolith response to head translation scaled by inverse target distance, adding to a semi-circular canal response to angular head rotation. Input to the canal branch of the model was taken from human angular head velocity recorded by magnetic search coils, while input to the otolith branch was taken from otolith translation simultaneously recorded by flux gate magnetometer. The single free parameter of otolith weighting was optimized to best fit the data.

The model was tested against experimental data from humans during: free standing, walking, running, and volitional head rotation; and during standing on: a platform sliding horizontally at 0. 2 Hz, and tilting at 0. 1 Hz with and without proprioceptive attenuation by a foam rubber cushion. Tasks were repeated with targets 500, 100, and 50 cm distant, both in light and darkness. The model accurately predicted observations for nearly all tasks and conditions. Near targets required greater otolith weighting, consistent with greater weighting of otolith input for near viewing found in studies employing imposed whole body yaw. Otolith weights were similar with visible targets and in darkness.

The model failed only during volitional pitch and yaw, and for vertical motion (pitch and bob) during posturography while standing, sliding, and tilting with proprioceptive attenuation. The model accurately predicted the response during both passive whole-body rotation and quasi-natural movement with the head unrestrained, implying that the VOR operates similarly in both situations. Factors such as vision, proprioception, and efference copy absent during whole-body rotation appear unimportant to gaze stabilization during ambulation and compensation of postural perturbations. The model failed for volitional head rotation, implying that here eye movement is dominated by non-vestibular factors. Linearity of canal-otolith interaction was examined by re-analysis of the observed whole body rotation data constraining the model. Normalized otolith-mediated gain enhancement was determined for each rotational axis, disclosing only minor non-linearities in canal-otolith interaction at frequencies above 1. 6 Hz and when the rotational axis was posterior to the head.

We conclude that linear canal-otolith interaction is a useful model for the human VOR under a wide range of ecologically salient conditions.

SP8.4
A gaze control hypothesis: head-eye interactions account for observed kinematics
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Visual orienting movements made when the head is unrestrained are typically accomplished by coordinating movements of the eyes and head. When the head makes a

significant contribution to the overall gaze shift, eye movement kinematics can be dramatically altered compared to matched movements made in the absence of a head contribution. For instance, when associated with a large head movement saccades typically have lower initial peak velocities often followed by a decline in velocity and subsequent re-acceleration. This results in saccade velocity profiles with pronounced shoulders or secondary velocity peaks (Cullen and Guitton, 1997; Freedman and Sparks 2000, 1997; Phillips et al. 1995; Roy and Cullen 1998; Tomlinson and Bahra, 1986; Tweed et al. 1995). The development of two peaks in saccade velocity profiles depends primarily on the amplitude of the associated head movement and to a degree the relative timing of eye and head movements (Freedman and Sparks 2000).

The model presented here (a 2-dimensional extension of Freedman, 2001) accounts for head and eye movement kinematics by proposing an interaction between head velocity commands and the (separate) saccadic burst generator. The model does not utilize feedback control of gaze amplitude. Rather, a gaze signal is decomposed upstream from dynamic elements. A desired eye displacement signal serves as input to a classical saccadic controller (after Becker and Jürgens, 1990). A separate head displacement signal serves as input to a head burst generator circuit. Despite the lack of gaze feedback and the low VOR gain during gaze shifts, this model does produce normometric gaze shifts in response to head perturbations by using a simplified version of a model of neck reflexes (Peng et al. 1996).

Gaze shifts can be made to targets that are displaced vertically and horizontally. Data from the head unrestrained subject indicate that horizontal head movements can alter the kinematics of both the horizontal and vertical components of associated saccades. These data may be difficult to reconcile with some common-source models; cross-coupled models may need fewer modifications to account for the data. The original 1-dimensional gaze model has now been extended to include movements in two dimensions.

In the figure, horizontal (A,C, E) and vertical (B,D, F) velocities are plotted as functions of time. The upper 4 panels illustrate the effects of head movements on saccade components using two types of cross-coupling. In panels E and F, behavioral data are illustrated. Within the context of the Freedman (2001) model, neither error-coupling (Becker and Jürgens, 1990) nor output-coupling (Grossman and Robinson, 1988) in isolation can account for observed effects of head movements on saccade kinematics.

SP8.5
Modelling gravity-induced changes in position and orientation of listing's plane
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Head position with respect to gravity changes the dependence of ocular torsion on horizontal and vertical eye position, i. e. , it modifies the position or orientation of Listing's plane. These changes are transmitted by otolith afferents, the pathways of which are yet unknown. In a first attempt to model the underlying neural mechanisms (Glasauer et al. , J. Neurophysiol 86, 1546-1554, 2001), we proposed that pathways carrying otolith information reach structures involved in generating the saccadic burst so that post-saccadic positions follow Listing's law. However, due to the leakiness of the torsional velocity-to-position integrator in the brainstem, the same otolith information must also be transmitted to the neural integrators located in brainstem and cerebellum.

Using the model, we were able to propose a hypothesis for the generation of pathological central positional nystagmus, as seen in neurology as persistent nystagmus which only occurs in off-vertical head positions. The proposed parallel pathways influencing burst generation and velocity-to-position integration underline an important issue of the oculomotor system: the three-dimensional coordination of saccade generation and gaze holding. Therefore, the present model extends this issue in focussing on how cerebellar function may achieve two linked features of the neural brainstem integrators: the prolongation of the time constant of gaze holding and the matching of the two coordinate systems implemented in the saccadic burst generators and the neural integrators. We were further able to show that simulated damage to this proposed cerebellar mechanism captures the main features of another oculomotor disorder, downbeat nystagmus. (Supported by Fritz Thyssen Stiftung and Deutsche Forschungsgemeinschaft SFB 462, A5)

SP8.6
A model of efferent-mediated limit-cycle behavior
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While studying efferent-mediated rotational responses in the chinchilla vestibular nerve , we encountered afferents showing oscillations in their background discharge. The oscillations could be large with amplitudes of 100 spikes/s or more, could be damped or undamped, and could have periods of several minutes. Oscillations were seen in irregular, but not in regular, units and were observed in decerebrate, but not in anesthetized, animals or after vestibular-nerve section. Fluctuation amplitudes in individual neurons were correlated with the sizes of their efferent mediated rotational responses. Oscillations may reflect a loop involving feedforward afferent-to-efferent excitation (Plotnik et al. J Neurophysiol ,in press) and feedback efferent -> afferent excitation (Goldberg and Fernández J Neurophysiol 43: 986; Marlinski et al. in preparation).

To simulate the loop, we developed a nonlinear model consisting of three variables: 1) an afferent response (x) with instantaneous dynamics; 2) adaptation (y); and 3) efferent feedback (z). Afferent response is govened by the nonlinear equation

$$x = r_{MAX}x_S /(x_{1/2}+ |x_S|) \tag{1}$$

x_S is the afferent's synaptic input, r_{MAX} is the maximal response, and $x_{1/2}$ is the input leading to a half-maximal response. x_S was calculated from

$$x_S= x_{AFF} - g_A y + g_E z \tag{2}$$

where x_{AFF} is the hair-cell input and g_A and g_E are the adaptation and efferent gains, respectively. Dynamic equations for y and z

$$dy/dt = (1/_A)(-y + x) \tag{3}$$

and

$$dz/dt = (1/_E)(-z + x) \tag{4}$$

were solved by a fourth-order Runge-Kutta algorithm and values substituted into equation 2.

All three processes are necessary to produce oscillations. In the absence of adaptation, discharge saturates, rather than oscillates. When efferent feedback is removed, firing is stable at a level determined by x_{AFF} and y. There is one stationary point in the model. For sufficiently large values of efferent feedback gain (g_E), the point is unstable. To prevent the rate from increasing indefinitely, the instability has to be coupled to a saturating nonlinearity (e. g. , equation 1), in which case limit cycles occur. As feedback gain is lowered, the amplitude and period of the limit cycles diminish. Lowering feedback gain still further results in damped oscillations and finally in overdamped responses. An important aspect of the simulation is that the period of limit cycles is much longer than the kinetics of the underlying processes.

SP8.7
A model to explore the relationship between tilt/translation discrimination and velocity storage
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Movement in a gravitational field poses certain computational demands in terms of inertial motion estimation. A particular complication in this regard is that inertial forces and gravity cannot be distinguished by their physical actions on the otolith organs (Einstein's equivalence principle). Nevertheless, despite ambiguous primary otolith information the motor responses to head tilts and translation are different. It has been shown in the primate oculomotor system that a sensory convergence of semicircular canal and otolith signals is essential to distinguish gravitational from inertial components of linear acceleration at higher frequencies (>0. 1 Hz). Currently, however, the neural correlates for resolving the tilt/translation discrimination problem remain unknown. A recent investigation of the activities of vestibular-only neurons (VO) in the primate vestibular nuclei demonstrated that the rotational maximum sensitivity vectors of neurons sensitive to both rotational

and translational stimuli are scattered throughout 3D space, indicating a strong convergence from multiple canal pairs. The majority of these neurons responded to both translation and head tilt; however, some distinguished between the two stimuli. VO neurons that responded exclusively to head rotations encoded head velocity in a specific semicircular canal plane.

We present a sensory convergence model that combines canal and otolith sensory information in a feedback network of VO neurons around an internal representation of the canal dynamics to provide tilt/translation discrimination. This first sensory processing stage is cascaded with a previously proposed feedback network of eye-movement-sensitive vestibular neurons that provide the motor drive for horizontal eye movements during rotations and translations. The model simultaneously reproduces the effect of "velocity storage" when the axis of rotation is aligned with gravity and discriminates roll tilt from interaural translation signals to produce appropriate horizontal eye movements at high frequencies (>0. 1 Hz). In contrast to other computational investigations of tilt/translation discrimination, we explore the problem in a more physiologically relevant context by incorporating several VO cell types within the proposed model structure. The ability to replicate the basic characteristics of experimentally observed cell responses is demonstrated. Furthermore, we illustrate that the integrative properties of the velocity storage network itself can be used to transform rotational information into an appropriate dynamic estimate of head orientation relative to gravity.

We propose that a primary function of the velocity storage integrator system may be to provide such an estimate. Many of the low-frequency behavioral observations linked to velocity storage may arise as a side effect of a role for the velocity storage integrator in high frequency estimation of head orientation.

SP8.8
Modelling the orientation and gain of the vestibulo-ocular reflex as the output of three channels
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When humans or animals are passively rotated in the dark, the vestibulo-ocular reflex (VOR) is evoked comprising nystagmoid eye movements with slow phases that tend to compensate for the rotation and maintain the gaze on a fixed point in space. However neither the amplitude nor the orientation of the VOR alone is exactly correct to compensate for the movement and thus gaze is not actually kept constant. The variations in orientation and gain of the VOR vary with several factors such as proximity of viewing, vergence and eye position, but a predominant determinant of the VOR's performance is the axis of rotation that evokes it.

We have modelled the stimulating-axis-related variations in gain and orientation of the vestibulo-ocular reflex as the output of a three-channel system for each eye. Evi-

dence obtained before has led us to postulate a particular configuration for these channels. Our proposed configuration comprises two approximately orthogonal channels arranged as an X close to Listing's plane with a third channel roughly orthogonal to these two, about 10 degs temporal from straight ahead.

In this modelling session we will present an implementation of our three-channel model that shows the orientation and gain of the VOR evoked in each eye by rotation around any axis. We illustrate both the normal VOR and the consequences of visually induced gain changes around any axis. Responses are calculated by projecting the stimulation onto the three channels, multiplying each by a predetermined gain and expressing the output as the vector sum of the channels' activity. Gain changes are simulated by projecting the adapting stimulus onto our postulated channels and adjusting the gains in proportion to their evoked activity.

No attempt has been made to implement any of the dynamic properties of the VOR in this model. By using a single gain for each channel we restrict ourselves to the pass-band of the VOR.

SP8.9
A dynamic model for the vertical VOR, OKR and visual-vestibular interactions in the primate

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A quantitative dynamical model was constructed to aid in the understanding of the roles of the cerebellum and other neuronal sites in the performance and adaptation of the vertical vestibuloocular reflex (VOR). The model structure was based upon the known neuroanatomy, consisting of a pathway which passes through flocculus (FL pathway) and one which does not (nonFL pathway). The FL pathway was further divided into a subsystem which includes the pathway from sensory input to flocculus (preFL&FL subsystem) and a subsystem which includes the pathway from flocculus to motor output (postFL subsystem). Also, the preFL&FL subsystem and the nonFL subsystem in which multi-modal signal processing is executed were divided into subsystems each of which represents signal processing for a single modality (vestibular, visual, efference copy).

Characteristics of each subsystem were described as a transfer function. Model parameters were estimated by fitting model outputs to eye movements and cerebellar flocculus Purkinje cell firing patterns that were recorded in naïve squirrel monkeys during VOR enhancement (VORe) in which the optokinetic stimulus moved in the opposite direction of head rotation. The optokinetic and vestibular stimuli consisted of the sum of five different sinusoids (0. 05, 0. 27, 0. 5, 1. 27, 2. 5Hz). The model can reproduce eye velocity and flocculus Purkinje cell firing patterns during VORe, and can correctly predict these values during VOR in darkness, optokinetic response (OKR), and visual-vestibular mismatch paradigms consisting of a different single frequency (0. 1, 0. 5 or 2. 5Hz) or sum-of-sinusoids.

The model can also predict eye velocities after flocculectomy when the monkeys' ability to suppress and enhance the VOR and follow visual targets is degraded; [VOR in darkness is much less affected by flocculectomy.]

Therefore, the model is valid to evaluate the roles of the cerebellum and other neuronal sites in the performance of the vertical VOR, OKR and visual-vestibular interactions within the stimulus range employed. The model may also be used to test different learning algorithms at different learning sites with different error signals for the vertical VOR motor learning task. (The model was implemented and simulated in the Matlab (Mathworks) Simulink environment.)

SP8.10
Constraints imposed on a predictive model of gaze shifts by adaptive changes observed following canal plugging

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The time course of natural head-unrestrained gaze shifts can be divided into two epochs. In an intact animal, the initial phase is driven by the saccadic burst generator. During the second phase, when the eye counter-rotates (to compensate for the continuing head motion), eye velocity is effectively controlled by the vestibulo-ocular reflex (VOR) (as the counter-rotation ceases when the head movement is experimentally interrupted). Our model assumes little dynamic interaction between the control of eye and head movement: both are triggered together and then run out their course nearly independently. A conventional internal feedback loop drives the saccadic eye movement. The model proposes that the duration of the saccadic phase is stretched and its velocity reduced by parametric control of the burst generator (possibly through a breaking pulse from the caudal fastigial nucleus). The duration is adjusted until the head contribution at the time when the eye approaches the orbital limit will bring the line of sight in the vicinity of the target. In addition, the gain of the VOR is titrated by a gaze error signal during the transition from the saccadic phase, resulting in small gaze slides.

In animals with plugged semi-circular canals, gaze shifts still exhibit counter-rotations of the eye, which continue when the head motion is unexpectedly arrested, despite the absence of peripheral vestibular signals. Recording in the paramedian pontine reticular formation indicates that the saccadic phase ends as the eye reverses direction in an attempt to match the velocity of the eye to that of the head. To simulate the counter-rotations after canal plugging, our model replaces the vestibular afferent signal with an internal prediction of head velocity. However, it deliberately underestimates the actual head velocity, giving rise to the prolonged gaze slide seen after plugging. Our model includes another predictive mechanism to coordinate the contribution of the two phases to the completed gaze shift. The amplitude of the command to the

burst generator also is reduced to allow the line of sight to reach the target at the end of the gaze shift despite the gaze slide following the saccadic phase.

SP8.11
Modeling tilt and translation responses in humans using observer theory
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All linear accelerometers measure gravito-inertial force, which is the sum of gravitational force (tilt) and inertial force due to linear acceleration (translation). Neural strategies must exist to elicit tilt and translation responses from this ambiguous cue. To investigate these neural processes, we developed a model of human responses [1] and simulated a number of motion paradigms used to investigate this tilt/translation ambiguity. In this model, the separation of GIF into neural estimates of gravity and linear acceleration is accomplished via an internal model made up of 3 principal components: 1) the influence of rotational cues (e. g. , semicircular canals) on the neural representation of gravity, 2) the resolution of gravito-inertial force into neural representations of gravity and linear acceleration, and 3) the neural representation of the dynamics of the semicircular canals. By combining these simple hypotheses within the observer theory framework, the model mimics human responses to a number of different paradigms, ranging from simple paradigms, like roll tilt, to complex paradigms, like post-rotational tilt and centrifugation. It is important to note that the exact same mechanisms can explain responses induced by simple motion as well as by more complex motion paradigms; no additional elements or hypotheses are needed to match the data obtained during more complex paradigms. Therefore, these modeled response characteristics are consistent with available data and with the hypothesis that the nervous system uses internal models to estimate tilt and translation in the presence of ambiguous sensory cues. Supported by NIDCD grant DC04158.

[1] Merfeld DM, Zupan LH (2002) Neural processing of gravito-inertial cues in humans. III. Modeling tilt and translation responses. J Neurophysiol 87:819-833.

SP8.12
Modeling of the horizontal angular vor evoked by high-acceleration rotations in the squirrel monkey
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Our studies of the horizontal angular VOR evoked by high-frequency, high-acceleration head movements in squirrel monkeys have revealed two response components. The mathematical model we developed to describe these components receives inputs from linear and nonlinear pathways. The linear pathway has a constant gain over the range of rotational frequencies from 0. 5 - 15 Hz at velocities of 20 - 150deg/s. This pathway provides the principal input to the angular VOR in animals with intact vestibular

function and in the absence of any optically-mediated requirement for a change in the gain of the reflex. The non-linear pathway has phasic response dynamics and a gain that rises with the cube of head velocity for rotational frequencies > 2 Hz and head velocity > 20 deg/s. This pathway is also rectified in that it is rapidly driven into inhibitory cutoff.

We have used this model with coefficients derived from animals with intact vestibular function under normal viewing conditions to predict changes in the VOR after unilateral vestibular lesions (labyrinthectomy or canal plugging) and after spectacle-induced adaptation. The model described in this abstract was used to perform the following simulations of data obtained in these experimental conditions.

The responses following adaptation to magnifying (2. 2X) spectacles are modeled by increasing the gain of the linear pathway by 1. 7X and by increasing the gain of the nonlinear pathway by 4. 0X. The responses following adaptation to miniaturizing spectacles (0. 45X) are modeled by decreasing the gain of the linear pathway by 0. 7X and by decreasing the gain of the nonlinear pathway to 0. For both responses, the dynamics of the linear pathway are modulated by a central adaptation element reflecting the low-pass filter characteristics of the adaptation process.

Ipsilesional responses and contralesional responses following unilateral labyrinthectomy are modeled by removing inputs arising from the lesioned side. Changes occurring with vestibular compensation are modeled by increasing the gain of the linear pathway on the intact side by 1. 6X and of the nonlinear pathway by 4. 0X. In this model, the asymmetry between ipsi- and contralesional responses arises because the nonlinear pathway is driven into inhibitory cutoff during ipsilesional rotations. (Supported by NIH R01 DC02390)

SP8.13
Biophysical basis of spike frequency modulation
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Spike frequency modulation is clearly of paramount importance in the network properties of the vestibular system. This modeling effort will quantitatively analyze the relationships between spike frequencies and underlying membrane potential. Since vestibular neurons show a range of excitability properties that reflect differences in their intrinsic voltage dependent conductances, we will compare the differences in the dependency of spike frequency modulation on the level of depolarization for different types of model neurons. This will include models for Type A and Type B neurons of the medial vestibular nucleus, which are thought to mediate in part static versus dynamic properties, respectively.

Both the linear and non-linear behavior of the models will be explored using small signal white noise and large amplitude step or ramp stimuli. In addition, we will show that under certain conditions spike frequency modulation can be predicted by the linear response of the neuronal

model. However, there are other conditions in which this cannot be done and criteria will be presented to distinguish between these two situations.

An inherent problem in spike frequency analysis is the determination of the phase or delay of the measured instantaneous frequency compared to the analog stimulus. This problem is intrinsic to the differences caused by the use of an input analog stimulus and an output digital signal. The usual procedure of assigning time at end of the interval used in the measurement of the instantaneous frequency introduces an artificial delay or phase lag. Low pass filtering of the spike frequency is a useful approach, but also leads to some phase distortion.

These issues will be discussed with regard to the evaluation of model systems using spike frequency experimental data. It will be shown that both the membrane potential and spike frequency modulation show resonant or band-pass characteristics, which are important for the network behavior that mediates both static and dynamic signals.

SP8.14
Neck reflex stabilization in a three-dimensional head model

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The biomechanics of the head and neck pose an intrinsically unstable system. The head is an eccentric mass balanced on top of the cervical column, a relatively narrow base of support. Most movements of the head place its center of gravity beyond the support perimeter. Head posture, however, is maintained through coordinated neck muscle activity, dependent on the planes of motion, the musculoskeletal anatomy, and the sensory inputs to the neck. Previously, we developed homeomorphic models of the head in the horizontal (yaw) and sagittal (pitch) planes of movement, and predicted the mechanical, vestibular and proprioceptive contributions to head stabilization. We are now developing a three-dimensional biomechanical model of the head for the purpose of determining the dynamics of the neck reflexes in three-dimensions.

A three-dimensional rigid-body model of the head rotates around a spherical joint (three-degrees of freedom) and is slightly posterior to the head center of mass. Passive biomechanical parameters of this model are based on anthropomorphic data, used for crash-test models. The initial dynamics of the neck reflexes, composed of the vestibulo-collic reflex (VCR) and the cervico-collic reflex (CCR), are based on our previous models. Initial reflex dynamics are then adjusted to experimental data. We applied horizontal plane, yaw 400-600°/s2 (±20-30°) perturbations to the trunk. Seated subjects were asked to fixate a stationary target in space, an imagined target, or perform mental distraction tasks in the dark. Three-dimensional eye and head orientations were recorded using a magnetic search coil

system. Data were collected from 6 patients with bilateral vestibular deficit (BVD), 6 patients with unilateral vestibular deficit (UVD) and 7 normals subjects.

Model simulations, constrained to head movements in the horizontal plane compared well with experimental data. Larger head oscillations were produced during trunk perturbations towards the lesioned sides (1000-2000°/s2, ±3-8°) than towards the non-lesioned sides (500-1000°/s2, ±1-2°). These head oscillations result from a deficient VCR. As predicted by our model, the VCR is required to prevent head oscillations at the natural frequency of the head. Pitch and roll components of the head response required additional reflex controllers to counteract the force of gravity in these planes of motion. (Supported by NIH Grant DC00979 and The Clare Boothe Luce Foundation)

SP8.15
Model for identification of the vestibular contribution to human postural control

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A relatively simple feedback control model of human quiet stance control was developed to describe the dynamic characteristics of body sway evoked by external perturbations, such as rotation of the support surface and/or visual surround. Experimental results revealed that body sway responses to these stimuli were quite linear for any given stimulus amplitude. But overall, responses were nonlinear in that the amount of body sway evoked strongly depended on the stimulus amplitude. The hope was that modeling could explain this overall nonlinear behavior.

We found that a relatively simple model was able to explain a large portion of our experimental results. The subject's body was modeled as a single-link inverted pendulum. An inverted pendulum is inherently unstable, requiring application of an appropriate corrective torque to maintain stability. The corrective torque must include at least 2 components; one proportional to the deviation of body sway position (a stiffness component), and the other proportional to body sway velocity (a damping component). We assumed that a weighted combination of sensory information from vestibular, visual, and proprioceptive sources provided the position and velocity information necessary for the generation of corrective torque. A time delay was included to account for latencies in sensory transduction, transmission, central processing, and muscle activation. These model components were organized into a negative feedback arrangement that formed a position control system.

Model parameters were estimated from nonlinear curve fits of the model's transfer function equation to experimentally derived gain and phase data spanning a frequency range of 0. 016 to 2. 2 Hz. This position control model was able to explain dynamic behavior over a frequency range of about 0. 1 to 1. 2 Hz. Lower frequency behavior (<0. 1 Hz) could not be explained by this position feedback control model alone, but with the addition of a

force feedback component operating in a positive feedback mode, the model was able to account for low frequency behavior. Curve fit results showed that the vestibular contribution (vestibular sensory weight) to balance control changed as a function of environment/stimulus conditions. At low stimulus amplitudes, vestibular orientation cues made only a small contribution to balance control (<15% depending on test conditions). At higher stimulus amplitudes, responses were dominated by vestibular cues (~80%). Thus, the model-based interpretation of experimental results revealed the presence of sensory reweighting as the source of the overall nonlinear behavior of the postural control system.

SP8.16
Biomechanical models of the semicircular canals
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Biomechanics plays an important role in tuning the sensitivity of the semicircular canals to angular acceleration stimuli, decomposing the 3D motion into vectorial components carried by canal nerve branches, and preprocessing the temporal waveform prior to mechano-transduction by hair cells. We have developed a series of morphologically descriptive models, for both normal and pathological conditions, to study the mechanics of isolated single canals as well as the coupled three-canal labyrinth. The single-canal model addresses macromechanics responsible for temporal responses of the cupula volume displacement to angular head movements. The three-canal model addresses directional coding in three-dimensional space. This model was recently extended to address the biomechanical origin of gravity-dependent semicircular canal responses observed under pathological conditions of canalithiasis and cupulolithiasis. This was done by including the forces resulting from calcium carbonate debris (particles) moving within the canal lumen and/or adhered to a cupula.

Results are relevant to the origin and treatment of Benign Paroxysmal Positional Vertigo (BPPV). The labyrinthine fluids were simulated using the Navier-Stokes equations subject to appropriate viscous and kinematical boundary conditions arising from the fluid-solid interaction with the membranous labyrinth, cupula and particles. The coupled equations were solved numerically to determine the endolymph volume displacement, cupulae displacements, and particle movements in response to head movements and/or changes in gravito-inertial acceleration [Supported by NIDCD PO1 DC-01837 and NSF IBN-9816921].

SP8.17
During gaze shifts, brainstem saccadic neurons are modulated in real-time by head movement signals
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How the brain coordinates eye and head movements to shift the axis of gaze relative to space remains a topic of debate. To date, two general classes of gaze control models have been proposed. First, gaze accuracy could be achieved by comparing a desired change in gaze position signal with the actual change in gaze position (gaze feedback). Alternatively, the desired change in gaze position signal could be decomposed into eye and head components, and separate feedback loops would control the eye and head movements (separate feedback). In the present study we combined experimental and theoretical approaches to compare these model structures.

First, we utilized a precision torque motor to deliver highly reproducible perturbations (40ms after gaze shift onset, duration: 35ms, peak: 150 deg/s) to the head of two macaque monkeys during gaze shifts while simultaneously recording the activity of brainstem excitatory and inhibitory burst neurons (BNs) or omnipause neurons (OPNs). The perturbation produced a gaze deceleration that did not stop the movement or affect its accuracy, lengthened the gaze shift duration by ~45ms, and only marginally changed the eye trajectory (suggesting that the gain of the VOR was reduced). Strikingly, we found that the duration of OPN pauses, as well as BN bursts, also increased during perturbed gaze shifts. In fact, for all neurons tested, the linear relationship between the gaze shift duration and the pause or burst duration was statistically the same in both conditions. In addition, 1) the discharge dynamics of BNs could not be described using an eye velocity-based model estimated during saccades, especially toward the end of the movement where the firing rate generally overshot the model prediction, 2) BNs exhibited a head velocity-related transient decrease in activity immediately (<5ms) following the perturbation, and 3) the same undershoot of the saccadic prediction toward the end of gaze shifts was observed during perturbed gaze shifts. Thus, the spike trains of all neurons in the brainstem burst generator were influenced by externally applied head perturbations during gaze shifts.

We found that a slightly modified version of the dynamic gaze feedback model of Galiana and Guitton (1992) could account for our results. Specifically, the VOR gain was set to gradually resume to unity to mirror the time course of VOR interneuron discharges (Roy and Cullen 2002). In addition, BNs received a direct head velocity-related signal. This model was able to predict all of our key findings, including: the lengthening of discharge durations, the short-latency transient decreases in firing rate, as well as the undershoot of the saccadic prediction toward the end of the movements. (Supported by the Canadian Institutes of Health Research, the Fonds de la Recherche en Santé du Québec, and the Natural Sciences and Engineering Research Council.)

SP8.18
A model of the influence of canal, otolith and visual cues on spatial orientation and eye movements
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The sensory weighting model [1] is a general model of sensory integration that consists of three processing layers. First, each sensor provides the central nervous system (CNS) with information regarding a specific physical variable. Due to sensor dynamics this measure is only reliable over the frequency range that the sensor is accurate. Therefore, we hypothesize that the CNS improves on the reliability of the individual sensor outside this frequency range by using information from other sensors, a process referred to as "frequency completion". Frequency completion uses internal models of sensory dynamics. This "improved" sensory signal is designated as the "sensory estimate" of the physical variable. Second, before being combined, information with different physical meanings is first transformed into a common representation; sensory estimates are converted to intermediate estimates. This conversion uses internal models of body dynamics and physical relationships. Third, several sensory systems may provide information about the same physical variable (e. g. semicircular canals and vision both measure self-rotation). Therefore, we hypothesize that the "central estimate" of a physical variable is computed as a weighted sum of all available intermediate estimates of this physical variable, a process referred to as "multi-cue weighted averaging ".

The sensory weighting model is applied to three-dimensional (3D) visual-vestibular interactions and their associated eye movements and perceptual responses. The model inputs are 3D angular and translational stimuli. The sensory inputs are the 3D sensory signals coming from the semicircular canals, otolith organs and visual system. The angular and translational components of visual movement are assumed to be available as separate stimuli measured by the visual system using retinal slip and image deformation. In addition, both tonic ("regular") and phasic ("irregular") otolithic afferents are implemented. Whereas neither tonic nor phasic otolithic afferents distinguish gravity from linear acceleration, we hypothesize that the CNS might preferentially use tonic afferents to estimate gravity and phasic afferents to estimate linear acceleration. The model outputs are the internal estimates of physical motion variables and 3D slow phase eye movements. The model also includes a smooth pursuit module. The model matches eye responses and perceptual effects measured during various motion paradigms in darkness and with visual cues. Supported by ESA External Fellowship Program, and NIDCD grants DC04158 and DC04644.

[1] Zupan LH, Merfeld DM, Darlot C (2002). Using Sensory Weighting to Model the Influence of Canal, Otolith and Visual Cues on Spatial Orientation and Eye Movements. Biol. Cybern. 86:209-230.

SP8.19
Modeling the relation between head orientation, head movement and otolith responses in humans
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We have performed a finite element analysis of displacements of otolith membranes by linear accelerations. The simulations were based on accurate measurements of the surfaces of human utriclar and saccular maculae, which indicate a clear curvature of these surfaces. Our results show that this curvature, a feature probably found in all mammals, has no effect on the mechanics of the structure as a whole, since the elastic coupling between distant parts which is provided by the otolith membrane is insufficient. Hair cell excitations on any place of the macula are only affected by the local orientation of the macula with respect to acceleration. Based on the displacements of the otolith membrane, we also calculated the induced activation patterns on the otolith epithelia. These patterns provide for the first time a complete image of peripheral otolith activity. We were surprised to find small regions perpendicular to the striola where the excitation level changes rapidly over a short distance. The location and shape of these regions might provide an important cue for the determination of head orientation.

Different tests were performed to validate the simulations. First, the analytical solutions, which can be obtained for the idealized case of a flat otolith, are in good agreement with the numerical results for that case. Second, a comparison with the individual activation patterns at selected locations on the macula showed that our predictions correspond well with single cell recordings of actual peripheral otolith neurons. (This study was supported by DLR 50WB9940.)