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SS01-1
Neural Coding and Multimodal Interactions for Action and Perception
IMPACT OF LOCOMOTOR EFFERENCE COPIES ON VESTIBULAR SENSORY ENCODING
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In all vertebrates, self-generated body motion necessitates compensatory eye movements to avoid perturbation of visual processing. This evolutionary conserved motor action is traditionally ascribed to the transformation of visuo-vestibular sensory signals into extraocular motor commands. During rhythmic locomotor activity in Xenopus laevis, however, intrinsic efference copies arising from the spinal central pattern generator (CPG) are the dominant source for eye movement control during locomotion. Although the impact of the CPG feed-forward command during undulatory swimming in larval Xenopus matches the spatio-temporal specificity of sensory-driven vestibulo-ocular reflexes during passive body motion, the two different signals, i.e. from the sensory periphery and the spinal cord, do not summate during locomotor activity. When the spinal CPG is active, horizontal angular vestibulo-ocular reflexes resulting from concurrent head movements are actively suppressed, indicating a considerable peripheral and/or central attenuation of the underlying sensory-motor transformation. In this context, efferent neural projections to vestibular hair cells in the inner ear convey locomotor-timed rhythmic discharge during tadpole fictive undulatory swimming. The cyclic impulse bursts are directly driven by spinal locomotor circuitry and provide the sensory periphery with information about the duration, burst amplitude and cycle frequency of ongoing locomotor activity. However, the efference copy has a differential impact on the resting discharge of individual vestibular afferent fibers, but on average causes a 50% gain reduction in sensory signal encoding. This considerable attenuation is likely to prevent overstimulation by adjusting the encoding of sensory signals to altered stimulus magnitudes and reflects a context-dependent gating of inputs during self-induced motion.

SS01-2
Neural Coding and Multimodal Interactions for Action and Perception
NEURAL CODING AND MULTIMODAL INTERACTIONS FOR ACTION AND PERCEPTION
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Understanding how sensory pathways transmit information under natural conditions remains a major goal in neuroscience. The common view is that early vestibular processing is fundamentally linear, making it an attractive model for studies of sensorimotor integration. However, most previous studies have used artificial (e.g. sinusoidal stimuli) to quantify how neurons in this sensory system encode head motion through firing rate. Thus, a new approach is needed to understand how the vestibular system encodes the sensory inputs that are actually experienced in everyday life. Accordingly, in our recent work we studies the statistics of natural motion in humans and monkeys and found that neither follows a power law, but instead drop off more rapidly for frequencies greater than $\sim$ 2–7 Hz. Our work has further established how heterogeneities in the intrinsic neural variability of vestibular nerve afferents determine early coding strategies. First, irregular semicircular and otolith vestibular afferents more efficiently encode natural first order statistics of self-motion than their regular counterparts, suggesting that coding strategies used by the primate vestibular system have adapted to natural scene statistics. Second, our experiments using naturalistic stimuli

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have revealed that early vestibular pathways can actually use temporal coding to represent self-motion information. Specifically, irregular afferents reliably discriminate between different stimulus waveforms through differential patterns of precise ($\sim$ 6 ms) spike timing, while regular afferents transmit information through changes in firing rate. Importantly, post-synaptic central neurons also use precise spike timing to represent self-motion, suggesting a novel and important role for temporal coding towards ensuring accurate self-motion perception.

SS01-3
Neural Coding and Multimodal Interactions for Action and Perception
VESTIBULAR CONTRIBUTIONS TO SPATIAL MEMORY
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Our studies conducted over the last 15 years have demonstrated that a complete loss of vestibular function in rats (bilateral vestibular deafferentation or BVD) results in spatial memory deficits in a variety of behavioural tasks, such as the radial arm maze, the foraging task and the spatial T maze, and even deficits in other tasks such as the 5-choice serial reaction time task (5-CSRT task) and object recognition memory task. These deficits persist long after the BVD, and are not simply attributable to ataxia, anxiety, hearing loss or hyperactivity. In tasks such as the foraging task, the spatial memory deficits are evident in darkness when vision is not required to perform the task. Similar studies in humans using the virtual Morris water maze, also demonstrate that vestibular information is important for spatial memory in humans and recent epidemiological studies suggest that vestibular dysfunction is a major contributor to cognitive impairment in the aging population. The deficits in spatial memory tasks, in particular, suggest that the hippocampus becomes dysfunctional following BVD and other kinds of vestibular impairment, and this hypothesis is supported by the finding that both hippocampal place cells and theta rhythm are dysfunctional in BVD rats. Now that it is clear that the hippocampus is dependent on vestibular information, the challenge is to determine how this information is compared with other sensory information, such as visual information, within the hippocampus and how that comparison is used by the hippocampus in its interactions with other brain structures.

SS01-4
Neural Coding and Multimodal Interactions for Action and Perception
ADAPTATION AND CALIBRATION OF VESTIBULAR SIGNALS FOR BALANCE AND PERCEPTION
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What determines how a particular frequency-encoded vestibular signal is interpreted centrally?
Experiment 1. We examined perceptions of rotation evoked by galvanic vestibular stimulation (GVS) and by real whole-body rotation before and after 20-minutes of conditioning with random angular rotation. This conditioning markedly attenuated perceptions of rotation and GVS-evoked balance reflexes responses for at least an hour. Thus, prior movement modulates vestibular canal sensitivity.
Experiment 2. Subjects attempted to walk with eyes shut to a previously seen target. GVS that biased canal afferent firing made subjects turn towards the anodal side. If however, subjects received GVS during a walk with eyes open, they no longer deviated from the target with eyes shut. Is this down-regulation or recalibration of the canal signal? Subjects were pre-conditioned with GVS and vision but the GVS polarity was reversed when they shut the eyes. This caused a large turn consistent with recalibration of the canal signal representing zero turn rather than its down-regulation.
Experiment 3. To determine whether gain is similarly recalibrated, GVS was coupled to head angular velocity (roll) to increase the afferent response to rotation when standing. With eyes shut, balance was immediately unstable but on opening the eyes, stability was regained as GVS continued. After a minute they shut the eyes again and balance remained stable, only to became unstable when GVS was turned off.
These experiments reveal three forms of rapid plasticity and modulation of vestibular-evoked responses that could arise through peripheral influences, efferent modulation, or central vestibular processing.

SS01-5
Neural Coding and Multimodal Interactions for Action and Perception
VESTIBULAR PERCEPTUAL THRESHOLDS VARY CONSISTENTLY WITH AGE
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A number of earlier studies have come to different conclusions regarding the effect of age on vestibular thresholds. Given this variety of findings, we expanded upon the earlier studies by including a substantially larger number of healthy normal subjects (54 females and 51 males). We specifically targeted our recruitment to obtain age- and gender-matched subjects for each decade spanning an age range between 18 and 80 years of age. We measured direction recognition thresholds using a forced-choice paradigm combined with 1Hz single cycle sinusoidal acceleration stimuli for: (a) yaw rotations – transduced primarily by the lateral semicircular canals, (b) superior-inferior (z-axis) translations – transduced primarily by the saccular organs, (c) inter-aural (y-axis) translations – transduced primarily by the utricular organs, and (d) roll tilts – transduced primarily by the vertical canals and the utricular organs. We also repeated roll tilt stimuli using a frequency of 0.2 Hz. Methods mimic those we've used for previously published studies, so we provide just a few crucial methodological details. Motion direction was randomized. A three-down/one-up adaptive staircase was used to target stimuli near each subject's threshold, where near-optimal information is obtained. All motions were performed in complete darkness. A Gaussian psychometric function was fit to the data to determine each subject's threshold, defined as the standard deviation of the fitted Gaussian noise distribution. We found no significant effect of gender on the measured thresholds but found a consistent and significant affect of age. Specifically, thresholds increased roughly linearly with age above the age of 40 for all five motions tested; no significant changes were observed for subjects between the ages of 18 and 40. This age-effect explained about 20% of the variation measured in this data set. The pattern shown by these data does not match that predicted by vestibular hair cell and afferent neuron counts, which appear to decrease monotonically with age over the entire age range we studied. The cause of these age changes remains undetermined, but a metabolic-related cascade related to the free radical theory of aging could play a role.

SS02-1
Vestibular Periphery: Structure, Function and Restoration
EVOLVING VIEWS OF STRUCTURE IN THE VESTIBULAR PERIPHERY: REGIONS, MICRODOMAINS, AND ORGANELLES
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Central vestibular and oculomotor nuclei require input from the periphery. Peripheral endorgans are divided into central and peripheral regions with different morphophysiological characteristics. Traditionally, the striolar region in the vestibular otolith endorgans in vertebrates has been defined by lower hair cell density, complex calyces, and smaller otoliths, with the reversal line running down the middle. Recently, using calretinin immunohistochemistry, the central/striolar region in rodent utricular macula has been found to lie almost entirely medial to the reversal line, which has functional implications for low-gain calyx-only afferents. With regard to calyx endings, we have recently defined four microdomains in these endings, corresponding to the diverse functions they subserve (Lysakowski et al., J. Neurosci., 2011). Each microdomain has a set of voltage-gated ion channels, scaffolding and cell adhesion proteins. Considering the calyx thusly allows us to re-evaluate its purpose. We have also re-examined the striated organelle (SO, Vranceanu et al., PNAS, 2012), consisting of alternating thick and thin bands, located in the subcuticular region of hair cells. In type I hair cells, the SO is shaped like an inverted open-ended cone, contacting apical cell membrane, and separated from the cuticular plate (CP) by large mitochondria. Stereociliar rootlets bend at a 110° angle, traverse the CP and insert in plasma membrane opposite the kinocilium. Confocal and EM immunogold experiments, confirmed by co-IP/mass spectrometry, have demonstrated that antibodies to γ-actin, actin-binding proteins β-2 spectrin and α-2 spectrin, and actin-bundling proteins TRIObp and nebulin label SOs, and that SOs are absent in some stereociliar mutants.

SS02-2
Vestibular Periphery: Structure, Function and Restoration
PRIMARY VESTIBULAR NEURAL RESPONSES TO SOUND AND VIBRATION
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Normally guinea pig irregular afferents from the anterior canal do not respond to 500 Hz short tone burst sound (ACS) and vibration (BCV) – at least up to 130 dB SPL ACS or 3 g BCV. However continuous recording from many such canal afferents while a dehiscence was made in the bony canal showed that after the SCD, previously unresponsive canal afferents were activated and phase locked to brief ACS stimuli even at very high frequencies (up to 3000 Hz). This was not due damage because the neurons still responded to pitch angular acceleration.
These results imply that the enhanced fluid displacement to ACS after an SCD was sufficient to cause a previously non-responsive afferent to respond and they indicate that ACS works by causing fluid displacement (as Young et al 1977 suggested), which causes the short stiff hair bundles of type I receptors to be deflected and so the afferent neurons to be activated and phase-lock to the stimulus. These data are the physiological correlates of the enhanced oVEMP and cVEMP to ACS and BCV which has been reported in patients with SCD.
If after SCD a high frequency ACS stimulus (e.g $>$ 1000 Hz) is maintained for seconds, then following the initial excitation, most neurons are progressively inhibited. This response pattern appears to be due to the pulsatile fluid displacements causing the cupula to be deflected by an "impedance pump" mechanism since regular neurons from that canal show similar patterns of progressive silencing and return, without the phase-locked activation of irregular afferents.

SS02-3
Vestibular Periphery: Structure, Function and Restoration
THE ORIGIN OF AUDITORY SENSATION BY VESTIBULAR ORGANS
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Otolith organs were present in primitive fish hundreds of millions of years ago and provided auditory sensation well before the appearance the basilar papilla in amphibians, reptiles and birds. Although supplanted by the cochlea for auditory sensation in mammals, the saccule and utricle have maintained the ability to respond at acoustic frequencies. The most sensitive vestibular afferent neurons, units with irregular discharge statistics in mammals, respond to acoustic stimuli with action potentials phase locked to a specific phase of the sinusoidal stimulus. We examined physical mechanisms responsible for sound-evoked deflection of sensory hair bundles in the utricle, saccule, and cristae under normal physiological conditions, and with a superior canal dehiscence (SCD). The approach used single unit recording, force measurements, and finite element modeling. Results implicate nonlinear mechanisms factors in SCD syndrome, vestibular evoked myogenic potentials, and responses of vestibular organs to pulsed ultrasound. [Supported by NIH R01 DC006685 & R01 DC012060]

SS02-4
Vestibular Periphery: Structure, Function and Restoration
THE RAPIDLY EXPANDING RANGE OF OPTIONS FOR RESTORING VESTIBULAR SENSATION
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The past two decades have witnessed a proliferation of basic, translational and clinical research directed toward improving the diagnosis and treatment of vestibular disorders. Practical results of this research that directly impact clinical outcomes already include improvements in clinical exam maneuvers, diagnostic algorithms, objective tests of semicircular canal and otolith end organ function, genetic tests, systemic and intratympanic pharmacologic treatments, and surgical procedures such as canal plugging for correction of superior canal dehiscence. On the near hori-

zon are vestibular and cochlear/vestibular implants, gene therapy to restore hair cell function, gene therapy to treat genetic diseases affecting the labyrinth, significantly enhanced rehabilitation techniques, and wide availability of relatively inexpensive and portable systems for posture/gait analysis and for binocular 3D video-oculography during highly repeatable canal-specific head rotations. In this lecture, I will review these recent developments, focusing on the expanding range of novel approaches to restoring or otherwise enhancing vestibular sensation, and then discuss expectations for the near- and long-term future of vestibular disorder management.

SS03-1
Vestibular Plasticity and Adaptation
INCREMENTAL VESTIBULO-OCULAR REFLEX GAIN ADAPTATION: EFFECTS OF BACKGROUND LIGHT AND INTENSITY
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Incremental vestibulo-ocular reflex (VOR) gain (eye-velocity/head-velocity) adaptation training increases the VOR response by a larger amount in a shorter period of time compared to conventional training that relies on a constant, large retinal image error signal to drive adaptation.
We sought to determine the effect of background light level and laser target intensity on VOR gain adaptation.
We tested 5 normal subjects over 10 separate sessions. For sessions 1–8, the background light level during adaptation training was: dark, 0.1, 0.2, 0.3, 0.5, 0.7, 1 and 475 lux. For sessions 9-10 the laser target intensity was halved with background at 0.1 and 0.3 lux. The adaptation training lasted 15 minutes and consisted of left/right active head impulses. The VOR gain was challenged to increment, starting at unity, by 0.1 every 90 seconds for rotations to one side (adapting) and fixed at unity towards the non-adapting side. We measured active and passive VOR gains before and after training.
Active and passive VOR gains were similar under the different lighting conditions. In the dark, the post-training VOR gain towards the adapting side was $\sim$ 14% higher than pre-training. At 0.1, 0.2, 0.3, 0.5, 0.7 and 1 lux the gain increase was 10%, 7%, 6%, 6%, 7% and 7%, respectively. At 475 lux, the VOR gain increase towards the adapting side was the same as the $\sim$ 4% increase towards the non-adapting side at all light levels.
Our data suggest incremental adaptation training increases the VOR gain when performed at or below 1 lux.

SS03-2
Vestibular Plasticity and Adaptation
THE ROLE OF THE EFFERENT VESTIBULAR SYSTEM IN VESTIBULO-OCULAR REFLEX GAIN ADAPTATION AND COMPENSATION
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The precise mechanisms underlying vestibular adaptation and compensation in mammals remain to be determined. The predominantly cholinergic Efferent Vestibular System (EVS), an extensive pathway from the brainstem to the inner ear that can modify peripheral vestibular organ output, could be involved in both forms of plasticity.
We investigated the vestibulo-ocular reflex (VOR) response before and after VOR adaptation training, and compensation after unilateral labyrinthectomy (UL), in control and α9-knockout mice, which have a compromised EVS.
We measured the VOR gain (eye-velocity/head-velocity) in 26 α 9-knockout mice and 27 CBA129 controls. Mice underwent: baseline testing, gain-increase adaptation (x1.5) or gain-decrease adaptation (x0.5) training that consisted of a 40 minute visual stimulus synchronized to horizontal whole-body rotations (0.5Hz, peak-velocity 20°/s). We also measured the VOR gain in 20 α 9-knockout mice and controls 1, 5 and 28 days after UL.
Adaptation (difference in VOR gain between gain-increase and gain-decrease adaptation as a percentage of gain-increase) was significantly reduced in α 9-knockout mice (17%) compared to controls (53%), a reduction of $\sim$ 70%. After 28 days, α 9 knockout mice had $\sim$ 50% lower gain for both ipsilesional and contralesional rotations compared

to control mice. Control mice regained $\sim 75\%$ of their baseline function for ipsilesional and $\sim 90\%$ for contralesional rotations. α 9 knockout mice only regained $\sim 30\%$ and $\sim 50\%$ function, respectively, leaving the VOR severely impaired for rotations in both directions.
Our results show that loss of alpha9-nAChRs severely affects VOR adaptation and compensation, suggesting that complimentary central and peripheral EVS-mediated adaptive mechanisms are needed to optimally drive vestibular plasticity.

SS03-3
Vestibular Plasticity and Adaptation
MULTIPLE TIMESCALES IN ANGULAR VOR ADAPTATION: AN OPPORTUNITY FOR REHABILITATION?
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The brain was shown to rely on memory processes having multiple timescales to face the problem of motor learning in both voluntary movements, such as saccades, and reflex responses, such as the VOR. Learning affects a forward sensory model in the cerebellum through highly adaptable states, which learn quickly from motor errors but have poor retention, and through more stable states that learn more slowly but have greater retention. Such approach allows both quick adaptation to novel environments, and maintaining a stable overall behavior without disrupting the learning built up by previous experiences.
Recent findings in rodents suggest that learning in the VOR may occur at different sites: within the cerebellum at the Parallel Fiber – Purkinje Cell synapse, and in the brainstem at the Mossy Fiber - Vestibular Nuclei synapses. The latter could be responsible for motor memory consolidation and may hence correspond to a long timescale of learning. Such consolidation in mice was shown to be critically dependent on post-training and rest periods rather than on training periods. The development of VOR rehabilitation paradigms focusing on the adaptation of such longer memory processes could enhance the recovery from vestibular pathologies.

SS04-2
Neurophysiology of Vestibular Disorders and Treatments
SET-POINT VESTIBULAR ADAPTATION: ELIMINATING SPONTANEOUS NYSTAGMUS
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A cornerstone of vestibular rehabilitation is exercise to improve dynamic vestibular function, i.e., promoting vestibular responses to head rotations that are of the correct amplitude, direction and timing relative to what is demanded by the dynamic characteristics of the head movement itself. Considerable attention has been focused on the neurophysiological mechanisms that underpin dynamic vestibular adaptation and on the applications to physical therapy for patients with vestibular deficits. Much less studied has been what is called set-point adaptation as a means to eliminate a tonic imbalance in, for example, the otolith system (ocular tilt reaction) or in the canal system (spontaneous nystagmus). Here we study set-point adaptation taking advantage of the sustained nystagmus that is induced in all normal subjects who are placed into a high field (7T) MRI machine. This sustained response in the MRI machine is possible because the magnetic field induces the equivalent of a constant acceleration of the head leading to the prolonged response. We have identified multiple time courses of set-point adaptation and also studied the influence of visual fixation on set-point adaptation. We compared the responses in the MRI machine to those during rotation on a vestibular chair at a constant acceleration and the results are largely comparable. MRI induced nystagmus becomes a powerful way to study how the brain rebalances its tonic levels of activity so that movements can be launched from a stable platform and hence be more accurate.

SS04-3
Neurophysiology of Vestibular Disorders and Treatments
VESTIBULAR LOSS AND COGNITION IN AGING ADULTS
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Vestibular function declines with normal aging. Numerous lines of evidence suggest that vestibular loss leads to cognitive decline, particularly of spatial cognition, which encompasses spatial orientation and navigation skills. This talk will review recent epidemiologic studies from our group which have found that vestibular loss in aging adults is specifically associated with reduced spatial cognitive skills, such as the ability to mentally rotate images or recall spatial relationships. Moreover, studies from our group showing higher levels of vestibular impairment among individuals with dementia will also be reviewed. An overarching hypothesis regarding the contribution of vestibular loss in aging adults to age-related cognitive decline and dementia will be presented.