

Plenary Lectures

PL01

MAGNETIC VESTIBULAR STIMULATION: AN UPDATE

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It has been known for decades that Individuals working next to strong static magnetic fields can feel disoriented and vertiginous. Roberts et al. suggested this was due to peripheral vestibular stimulation. Indeed, humans, mice, and zebrafish while inside a strong, static magnetic field, all demonstrate behaviors consistent with peripheral vestibular stimulation. The proposed mechanism for this effects involves a Lorentz force resulting from the interaction of a strong static magnetic field with naturally occurring ionic currents flowing through the inner ear endolymph into vestibular hair cells. The resulting force within the endolymph is strong enough to displace the lateral semicircular canal cupula, inducing vertigo and the horizontal nystagmus seen in normal mice and in humans. The sustained force is comparable to a constant head acceleration. Here we will review the proposed Lorentz force hypothesis, and use data from humans with unilateral labyrinthine loss to pinpoint the specific semicircular canals involved. We will take advantage of the sustained nystagmus in the magnetic field to study the adaptive responses that normally act to null a spontaneous nystagmus. We will also discuss some practical implications of magnetic vestibular stimulation.

PL02

MODULATION OF VESTIBULAR NEURONS BY ACUTE HYPOTENSION OR METABOLIC CHANGES

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Reduction of blood flow to the vestibular system causes nausea, dizziness, and other autonomic symptoms. We investigated the pathophysiological mechanism of hypotension-induced dizziness and the vestibulosympathetic pathways following acute hypotension. Activities in the vestibular nuclei (VN), nucleus tractus solitarius (NTS), rostral ventrolateral medullary nucleus (RVLM) and intermediolateral cell column of the middle thoracic spinal regions (IMC) were measured by electrophysiological and immunohistochemical methods following microinjection of glutamate receptor agonists or antagonists into the medial vestibular nucleus (MVN), RVLM and/or sodium nitropruside (SNP)-induced hypotension, in rats with sinoaortic denervation. Acute hypotension produced excitation of electrical activity in 2/3 of type I neurons and inhibition in 2/3 of type II neurons recorded in the MVN. Hypotension increased the expression of c-Fos protein in the NTS, RVLM, and IMC, which was abolished by pretreatment with glutamate receptor antagonists in the MVN. Microinjection of glutamate receptor agonists into the MVN increased the expression of c-Fos protein in the NTS, RVLM, and IMC. Systemic treatment with monocarboxylate transporter inhibitor augmented hypotension-induced expression of c-Fos protein in the MVN. Both microinjection of glutamate receptor agonists into the MVN or RVLM and SNP-induced hypotension led to increased blood epinephrine levels. Microinjection of glutamate receptor agonists into the MVN increased blood pressure. These results indicate that the vestibulo-spino-adrenal axis may be a key component of the pathway used by the vestibulosympathetic reflex to maintain blood pressure following hypotension. And lactate metabolism is a possible factor contributing to changes in vestibular nuclear activities.

PL03

SELF-MOTION PERCEPTION REQUIRES VISUAL AND VESTIBULAR INTEGRATION**Dora E. ANGELAKI***Department of Neuroscience, Baylor College of Medicine; Department of Electrical and Computer Engineering, Rice University, USA*

Navigation and spatial orientation are vital functions in our lives. Sensory information arises from the balance (vestibular) organs in the inner ear, as well as from visual optic flow and other sensory, motor and cognitive cues. As such, a fundamental aspect of our sensory experience is how information from different modalities is often seamlessly integrated into a unified percept. Both theory and behavioral studies have shown that humans and animals combine multiple cues, as well as prior experiences based on the statistics of our environment and our interactions with it, according to a statically optimal scheme derived from Bayesian probability theory. Using navigational heading perception tasks, we show how multisensory interactions improve precision, reaction time and accuracy. The latter is particularly important when navigational environments include independently-moving objects. We study both computational principles and their neural implementations in diverse subcortical and cortical circuits that process visual (optic flow) and vestibular (acceleration) signals.

PL04

ATTENTION-BALANCE INTERFERENCE**Joseph M. FURMAN***Department of Otolaryngology, University of Pittsburgh, USA*

Attentional processes, which represent a key aspect of cognition, interact with vestibular function and other aspects of balance. This lecture will first review the functional brain imaging data that support the neuro-anatomical bases for interactions between cognition, especially attention, and balance. Then, the results of dual-task experiments that combine a vestibular or balance challenge with an attention task will be reviewed. Experimental subjects for these studies have included healthy young controls, healthy older persons, and persons with vestibular abnormalities. The vestibular/balance challenges have included peripheral vestibular stimulation, upright stance, and gait. These studies have shown that attentional processes and vestibular/balance processes consistently interfere with one another especially in older persons and those with vestibular abnormalities. The clinical assessment and treatment implications of attention-balance interference will be presented.

PL05

NEURAL REPRESENTATIONS OF NATURAL SELF MOTION: IMPLICATIONS FOR PERCEPTION AND ACTION**Kathleen Elizabeth CULLEN***Department of Physiology, McGill University, Montreal, Quebec, Canada*

The loss of vestibular function due to aging, injury, or disease produces dizziness, imbalance, and an increased risk of falls – all symptoms that profoundly impair quality of life. In this talk, I will describe how the brain processes vestibular information in everyday life. In particular, our work has established how the brain combines vestibular and extra-vestibular cues – for example proprioceptive and premotor information to ensure accurate perception and behaviour. Notably, in response to unexpected motion, pathways that mediate postural reflexes are robustly activated to maintain balance. In contrast, during volitional movement, we find that same pathways are markedly suppressed at the level of both the cerebellum and vestibular nuclei. This suppression is functionally advantageous, since an intact reflex would be counterproductive to the intended movement. Moreover, when unexpected vestibular inputs becomes persistent for voluntary motion, as would be the case following vestibular loss, the mechanism underlying the suppression of the unexpected sensory input is rapidly updated to re-enable this vital distinction between self-generated and externally-applied stimulation. In addition, we have further established that the vestibular pathways mediating the vestibulo-ocular reflex encode head motion in a behaviourally-dependent manner. While head velocity is robustly encoded when the goal is to stabilize gaze, when the goal is to voluntarily redirect gaze, the efficacy of

this reflex pathway is suppressed by an efferent copy of the gaze command. Taken together, these findings advance our understanding the neural circuits underlying vestibular disease, thereby providing a basis for new translational approaches to restore sensory function.

PL06

DISORDERS OF HIGHER (CORTICAL) VESTIBULAR FUNCTIONS

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The bilateral organization and representation of the vestibular system in multisensory cortical areas and the vestibular dominance of the non-dominant hemisphere raise the question of how one global percept of motion and orientation in space is formed. The traditional classification of peripheral and central vestibular disorders lacks a third category namely disorders of “higher vestibular function” which may be caused by central as well as by peripheral vestibular lesions.

A concept of such disorders which involve cognition and more than one sensory modality will be discussed for three conditions: room tilt illusion, spatial hemineglect, and bilateral vestibulopathy all of which present with deficits of orientation and spatial memory.

The room tilt illusion and spatial hemineglect involve vestibular and visual function to the extent that both conditions can be classified as either disorders of higher vestibular or of higher visual functions. A possible way of separating these disorders in a first step is to determine whether the causative lesion site affects the vestibular or the visual system.

For the vestibular system this lesion site may be peripheral or central. The criterion of “higher function” is fulfilled if cognition or senses other than the primarily effected one come into play.

Besnard, S. et al (2016) *Frontiers in Integrative Neuroscience*

Brandt, T. et al (2014) *Frontiers in Integrative Neuroscience*;

PL07

THE OTOCONIAL PATHOLOGIES RELATED TO BPPV – A REVIEW

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Goal: This review is to understand what are the otoconial pathologies and their roles in the positional vertigo.

Method: This review is based on largely the author’s publication and up to date published papers concerning cell and molecular mechanisms involved in otoconia formation and malformation, maintenance, degeneration and detachment relevant to the otoconial pathology.

Discussion: While the exact cellular and molecular mechanisms involved in the formation of the otoconia are not fully understood, some mechanisms are now known with the advent of molecular techniques and gene-modified mice models. It is now believed that early otoconia formation require specific proteins synthesized by the supporting cells serving as nuclei and calcium ion is attracted to form mineralized otoconia. Number of essential proteins for the formation of the otoconia have been identified: otopetrine (Otop), NADH oxidase 3 (NOX3), Plasma Membrane Ca-ATPase (PMCA2), and head tilt (het) mutants lack otoconia. Otoconin-90 and -95 considered a principal otoconial matrix proteins. Otogelin is related to the acellular otoconial membrane. Pendrin (PDS) mutants exhibited deficient or malformed otoconia. It is hypothesized that among certain individuals, particularly among aging population, who has propensity to develop otoconial detachment is due to the reduced production of yet-to-be identified adhesion molecules anchoring otoconia gelatin layer to the sensory epithelium.

Conclusion: Loss of inter-otoconial adhesion molecules and adhesion molecules in the acellular gelatin layer will be the target for the biomarker discovery for identifying high risk group and potential future clinical application.

PL08

MODERN VESTIBULAR FUNCTION TESTING**Gabor Michael HALMÁGYI¹**, Leigh A MCGARVIE¹, Hamsih Gavin MACDOUGALL¹, Ian S CURTHOYS¹¹*Royal Prince Alfred Hospital and the University of Sydney, Australia*

In the last 5 years the easy availability of equipment for measuring video head impulse and vestibular evoked myogenic potentials has revolutionized the clinical assessment of vestibular function. It is now possible to measure and monitor the function of each of the 10 vestibular sensory regions individually. It is even possible to refer to an absolute age-adjusted gain range for each semicircular canal. With this easy availability comes the necessity for reproducibility and for ways to recognize technical errors and biological pitfalls. This lecture will focus on some of the more obvious mistakes that are made in vHIT and VEMP testing and recommend ways to avoid them.

PL09

THE EXPERIMENTAL FOUNDATIONS FOR NEW TESTS OF VESTIBULAR FUNCTION**Ian S CURTHOYS***Department of Psychology, University of Sydney, Nsw, Australia*

Extracellular single neuron recordings from primary otolith and semicircular canal afferents in guinea pigs are providing evidence about how new clinical tests of otolith function work, but also how semicircular canal dehiscence (SCD) affects canal and otolith receptors. Afferents from the anterior canal with irregular resting discharge are not activated by sound (up to 135 dB SPL) or vibration in healthy guinea pigs with normally encased bony labyrinths. However, if an SCD is made then the same semicircular canal neuron which was insensitive to sound or vibration before SCD now shows sensitive phase-locked activity for air-conducted sound up to >3000Hz. In light of evidence and modelling by Rosowski and others we suggest that the reason for this is that the SCD enhances fluid displacement and so canal (and otolith) neurons show phase-locked responses and lowered thresholds. Maintained high frequency stimulation elicits a sustained change in firing in anterior canal neurons. In some cases that appears due to maintained phase locking activating the cell on each cycle, since the activation ceases abruptly at stimulus offset. In other cases the sound appears to cause a maintained fluid displacement, by virtue of the sound causing a deflection of the cupula since it takes seconds (a cupula time constant) after stimulus offset to return to resting activity. This may be caused by sound inducing an “impedance pump” which deflects the cupula. These neural results appear to explain both the enhanced VEMP responses after SCD and the maintained nystagmus (Tullio phenomenon) to maintained sound stimulation.

PL10

ENDOLYMPHATIC HYDROPS OF MENIERE’S DISEASE: THE PAST AND THE FUTURE**Noriaki TAKEDA***Department of Otolaryngology, University of Tokushima School of Medicine, Japan*

The most important histopathological finding in Meniere’s disease is endolymphatic hydrops (EH). It has long been accepted that Prof. Hallpike in London first reported EH in patients with Meniere’s disease in 1938. But, in the same year, Prof. Yamakawa in Osaka independently discovered EH in the temporal bone specimen from Prof. Ogata, his colleague, who suffered from Meniere’s disease. Prof. Yamakawa had studied arsenic-induced ototoxicity in guinea pigs with Prof. Wittmaack in Hamburg. He reported EH as a reaction to arsenic labyrinthitis in 1929, which was previously called hydropische Degeneration by Prof Wittmaack in 1920’s. However, without degenerative changes, Prof. Ogata’s EH was quite different from hydropische Degeneration. Because Prof. Ogata showed nystagmus beating to the affected ear during vertigo attacks, Prof. Yamakawa hypothesized that the affected ear was irritated. He, therefore, proposed the term Reizhydrops (irritative hydrops) in Meniere’s patients.

For a long time, we could only observe EH in postmortem temporal bone studies, until Prof. Naganawa in Nagoya developed a cutting-edge technology to visualize EH on Gd-enhanced MRI in living patients with Meniere’s disease in 2007. It was revealed that almost all patients with Meniere’s disease showed EH on MRI. It was also reported that in some patients, the degree of EH decreased after endolymphatic sac surgery. However, EH visualized by MRI is not always consistent with symptoms of Meniere’s disease. The discrepancy may be resolved by further advance in imaging technique allowing distinction between Reizhydrops and hydropische Degeneration.