

## NEUROPHYSIOLOGY SUMMARY

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### INTRODUCTION

The terrestrial gravitational field serves as an important orientation reference for human perception and movement, being continually monitored by sensory receptors in the skin, muscles, joints, and vestibular otolith organs. Cues from these graviceptors are used by the brain to estimate spatial orientation and to control balance and movement. Changes in these cues associated with the tonic changes in gravity (gravito-inertial force) during the launch and entry phases of space flight missions result in altered perceptions, degraded motor control performance, and in some cases, "motion" sickness during, and for a period of time after, the g-transitions. In response to these transitions, however, physiological and behavioral response mechanisms are triggered to compensate for altered graviceptor cues and/or to adapt to the new sensory environment.

Basic research in the neurophysiology discipline is focused on understanding the characteristic features of and the underlying mechanisms for the normal human response to tonic changes in the gravito-inertial force environment. These studies address fundamental questions regarding the role of graviceptors in orientation and movement in the terrestrial environment, as well as the capacity, specificity, and modes for neural plasticity in the sensory-motor and perceptual systems of the brain. At the 2001 workshop basic research studies were presented addressing: neuroanatomical responses to altered gravity environments, the neural mechanisms for resolving the ambiguity between tilting and translational stimuli in otolith organ sensory input, interactions between the vestibular system and the autonomic nervous system, the roles of haptic and visual cues in spatial orientation, mechanisms for training environment-appropriate sensorimotor responses triggered by environment-specific context cues, and studies of sensori-motor control of posture and locomotion in the terrestrial environment with and without recent exposure to space flight.

Building on these basic research studies are more applied studies focused on the development of countermeasures to the untoward neurophysiological responses to space flight. At the 2001 workshop, applied research studies were presented addressing issues related to the use of rotational artificial gravity (centripetal acceleration) as a multi-system (bone, muscle, cardiovascular, and, perhaps, neurovestibular) countermeasure. Also presented was a clinical study reporting on a new rating system for clinical evaluation of postflight functional neurological status.

The neurophysiology group met first on Wednesday evening in a two-hour session moderated by Chuck Oman, Jon Clark, Tom Marshburn, and Jason Richards. The focus of this session was a discussion of the experiences of US astronauts participating in the Phase I (Mir Station) long-duration flight program. A draft manuscript on the subject authored by the moderators was distributed to all participants, and some novel video footage from the Mir station as well as the ISS was presented. The main platform session, which is summarized in the next section, lasted throughout most of the day on Thursday. The session was very busy, with little time for questions following each presentation, and insufficient scheduled break time. Nevertheless, the session was well attended and achieved its primary goal of presenting the scope and depth of the entire NASA-NSBRI neurophysiology research program to all of its participants.

### SUMMARY OF PRESENTATIONS

#### *Neuroanatomical Studies*

*Ross, MD and J Varelas. Synaptic Ribbon Plasticity in Utricular and Saccular Maculae: New Clues to Functions?*

Ross and Varelas presented cellular evidence of vestibular plasticity during space flight. They reported that utricular and saccular maculae differ completely in their responses to weightlessness. Their results confirmed previous findings of increased numbers of synapses in Type II hair cells of the utricular maculae, with Type I cells showing lesser increases. In the saccular maculae, however, they found that synapses in Type II cells remain relatively stable throughout flight and postflight, while Type I cells fluctuate.

*Holstein, GR and GP Martinelli. The Effect of Spaceflight on the Ultrastructure of Adult Rat Cerebellar Cortex.*

Holstein and Martinelli also presented cellular evidence of vestibular plasticity during space flight. They reported that changes observed in the ultrastructure of Purkinje cells from the adult rat cerebellar cortex harvested 24 hrs after shuttle launch suggest that space flight induces excitotoxic responses in Purkinje cells.

King, WM, W Zhou, and B Tang. *Responses of Eye Movement Related Vestibular Neurons to Linear Acceleration (poster)*.

King et al. reported that specific classes of neurons were identified in the brainstem of awake behaving monkeys that selectively process and transform otolith sensory inflow into an oculomotor command for gaze stabilization during translation. These central vestibular neurons, characterized by their discharge pattern and anatomical connections, transmit otolith signals that are modulated by gaze. They point out that unlike semicircular canal reflexes, eye movements produced by otolith-ocular reflexes depend on gaze direction and are inherently disjunctive.

Fermin, CD, RF Garry, YP Chen, and D Zimmer. *Effect of Microgravity on Afferent Innervation*.

Fermin et al. reported that some members of S100 Calcium Binding Proteins (CBP) family are expressed in vestibular afferents of chicken at 1g, and that the mRNA of certain mammalian CBP S100 isoforms share distribution characteristics with chicken isoforms. They further reported that the expression pattern changes following mechanical injury of vestibular afferents and suggested that gene expression and protein distribution of S100 CBP may be affected by altered gravity.

### **Otolith Ambiguity Studies**

Zupan, L, DM Merfeld, and K King. *The Influence of Visual Rotational Cues on Human Orientation and Eye Movements (poster)*.

Zupan et al. investigated how the central nervous system separates the otolithic measurement of gravito-inertial force into estimates of gravity and linear acceleration. They measured eye movements and subjective roll in human subjects during and after roll optokinetic stimulation about the subject's naso-occipital axis. They reported that, in addition to a torsional optokinetic after-nystagmus observed for all orientations, a horizontal after-nystagmus was observed to the right following clockwise stimulation and to the left following counterclockwise stimulation. They suggest that these observations are in agreement with the GIF resolution hypothesis that suggests that subjective tilt illusion will induce a non-zero estimate of interaural linear acceleration, and therefore a horizontal translational VOR even in the absence of "true" linear acceleration.

Wei, M, HH Zhou, and DE Angelaki. *Visually-Induced Adaptation of the Translational Vestibulo-Ocular Reflex*.

Wei et al. reported on an experiment addressing the issue of visually-induced learning in the resolution of gravito-inertial forces. Preliminary results during cross-axis adaptation of the translational vestibulo-ocular reflex in primates suggest that learning effects in the resolution of gravito-inertial forces are limited and probably more complex than originally thought.

Merfeld, D. *Influence of Sensory Integration on the Neural Processing of Gravito-Inertial Cues (poster)*.

Merfeld reported on plans for a future flight project (currently in definition phase) to investigate certain neural processes of sensory integration adapt when astronauts experience weightlessness. The specific processes to be studied are those underlying the use of rotational cues to interpret ambiguous gravito-inertial cues via internal models.

### **Vestiblo-Autonomic Studies**

Schlegel, TT, TE Brown, SJ Wood, EW Benavides, RL Bondar, F Stein, P Moradshahi, DL Harm, JM Fritsch-Yelle, and PA Low. *Orthostatic Intolerance and Autonomic Cardiovascular Changes after Parabolic Flight*.

Schlegel et al. reported that syndromes of orthostatic intolerance resembling those occurring after space flight were induced by a brief (2 hr.) parabolic flight. The mechanisms differed between vomiters and non-vomiters, and vomiting was associated with increases in R-R interval variability and carotid-cardiac baroreflex responsiveness, suggesting that the emetic reflex transiently increases resting fluctuations in efferent vagal-cardiac nerve traffic.

Moore, ST, G Clément, A Diedrich, I Biaggioni, H Kaufman, T Raphan, and B Cohen. *Inflight Centrifugation as a Countermeasure for Deconditioning of Otolith-Based Reflexes (poster)*.

Moore et al. reported on plans for a future flight study to confirm results from the Neurolab mission suggesting that in-flight centripetal accelerations may protect subjects from postflight orthostatic intolerance.

Kaufmann, HC, I Biaggioni, B Cohen, A Diedrich, M Gizzi, R Clark, F Costa, and D Saadia. *Vestibular Influences on Autonomic Cardiovascular Control*.

Kaufman et al. reported that forward acceleration in the naso-occipital axis (as sensed by the otoliths) increases sympathetic efferent activity in the peroneal nerve.

### **Spatial Orientation Studies**

*Cohen, B, G Clément, ST Moore, and T Raphan. Perception of Tilt (Somatogravic Illusion) in Response to Sustained Linear Acceleration During Space Flight.*

Cohen et al. reported results from the Neurolab mission suggesting that the somatogravic illusion induced by centrifugation is maintained in space. They found that the illusion of tilt increased as flight continued and depended on the magnitude of linear acceleration, suggesting that astronauts continue to assign the gravito-inertial acceleration as the spatial upright after adaptation to altered gravity.

*Parker, DE, HBL Duh, JO Phillips, and TA Furness. Self-Motion System Frequency Response: Implications for Cybersickness.*

Parker et al. examined the frequency response of the visual self-motion system and found a motion frequency where the summed response of the visual and inertial self-motion systems was maximized. Their data support the hypothesis that conflicting visual and inertial motion cues at this "cross-over" frequency would be more likely to elicit sickness than conflicting cues at a higher frequency.

*Oman, CM, IP Howard, T Smith, AC Beall, A Natapoff, JE Zacher, and HL Jenkin. STS-90 Neurolab Experiments on the Role of Visual Cues in Microgravity Spatial Orientation*

Oman et al. reported using a Virtual Environment to record the subjective vertical in 4 astronauts during flight. They found that astronauts became more dependent on dynamic visual cues, and some also on static visual cues. He also reported that the subjective vertical is labile and can influence figure recognition and shading interpretation.

*Oman, CM, IP Howard, WL Shebilske, and JS Taube. Visual Orientation in Unfamiliar Gravito-Inertial Environments.*

Oman et al. also described results of a collaborative NSBRI research project on human visual orientation cues in humans and animals. They reported that performance of humans in 3D spatial memory experiments correlates with ability to mentally rotate 2D and 3D objects, and improves with training. They also reported that parabolic flight studies of rat head direction cells show that cells continue to respond in 0-G, and occasionally show changes in preferred direction that correspond to visual reorientation illusion onset in humans.

*DiZio, P and JR Lackner. The Role of Gravito-inertial Force Background, Spatial Orientation and Contact Cues in Perturbations of Reaching Movements by Coriolis Forces.*

DiZio and Lackner reported that rapid adaptation to rotating artificial gravity environments is possible. They also reported that the motor effects of the rate of adaptation to Coriolis force perturbations are equivalent in 2g, 1g, and 0g force backgrounds, but disorientation and motion sickness elicited by head movements during body rotation are less severe in low force backgrounds. Finally they reported that non-supportive contact with the environment during voluntary movement is a critical orientation cue driving adaptation.

*DiZio, P and JR Lackner. Somatosensory Suppression of Re-Entry Disturbances (poster).*

DiZio and Lackner also reported on plans for a future flight study to assess the role of non-supportive contact with the environment (haptic inputs) during voluntary movement in spatial orientation and adaptation to altered gravito-inertial environments.

### **Context-Specific Adaptation Studies**

*Shelhamer, M, J Goldberg, LB Minor, WH Paloski, LR Young, and DS Zee. Context-Specific Adaptation of Gravity-Dependent Vestibular Reflex Responses (NSBRI Neurovestibular Project I).*

Shelhamer et al. reported that during parabolic flight the magnitude of gravito-inertial force can be used as a context cue for switching between adapted saccade states. They found evidence for retention of this adaptation after 8 months. They also reported that the gain of the translational LVOR can be made context-specific, using head tilt as a context cue and that saccadic eye movements can be adapted in a context-specific manner, using a number of different context cues. For interaural translations, they found head roll to be a more effective context cue than head pitch. Finally they reported that sensorimotor adaptation to head movements during short-radius centrifugation (23 rpm, 1 g at the feet) can be induced and retained for at least a week.

*Cohen, HS, JJ Bloomberg, C Roller, and AP Mulavara. Varied Practice and Response Generalization as the Basis for Sensorimotor Countermeasures (poster).*

Cohen et al. presented preliminary data demonstrating that variable context adaptation may result in more rapid adaptive responses to novel environments through response generalization. They also described a future ISS study being planned to develop sensorimotor training regimens that promote adaptive generalization of locomotor function as a means of facilitating the adaptive transition between gravitational environments.

*Paloski, WH, SJ Wood, GD Kaufman, FO Black, and MF Reschke. Spatial Reorientation and Sensory-Motor Balance Control in Altered Gravity.*

Paloski et al. described a future flight study that will examine the fragility of the postural readaptation response by challenging crewmembers during postflight recovery with unusual z-axis acceleration created using a short radius centrifuge.

### ***Posture and Locomotion Studies***

*Peterka, R.J. Characterization of Sensory Integration and Control Strategies that Regulate Human Postural Control in Changing Conditions.*

Peterka reported that the human balance control system relies predominantly on proprioceptive cues during quiet stance, but becomes increasingly reliant on graviceptor (vestibular) cues when balance is perturbed. He also showed that loss of vestibular function profoundly alters and limits a subject's ability to utilize his/her remaining visual and proprioceptive cues, suggesting that reinterpretation of vestibular cues following space flight might be expected to produce similar deficits.

*Bloomberg, JJ, AP Mulavara, C Miller, PV McDonald, CS Layne, J Houser, H Cohen, and IB Kozlovskaya. Locomotion After Long-Duration Space Flight: Adaptive Modulation of a Full-Body Head and Gaze Stabilization System.*

Bloomberg et al. reported that after space flight, astronauts show reductions in dynamic visual acuity during locomotion. These data, along with supporting ground-based studies, reveal the existence of a full-body, gaze stabilization system that exploits the multiple degrees of freedom available during locomotion to help maintain clear vision during body movement.

*Layne, CS, AP Mulavara, PV McDonald, CJ Pruett, and JJ Bloomberg. Maintaining Neuromuscular Contraction Using Somatosensory Input During Long Duration Spaceflight.*

Layne et al. reported that application of pressure to the feet of free-floating astronauts enhanced the stereotypical lower limb neuromuscular activation associated with rapid arm movements. This suggests that the plantar sensory inputs can be used to enhance motor unit activation and may therefore be used as a countermeasure to inflight muscle degradation.

*Wall, C and L Oddsson. Recovery Trajectories to Perturbations During Locomotion.*

Wall and Oddsson described a novel method to study perturbations of gait during steady locomotion by giving small (5–10 cm) disturbances to one foot during the support phase while recording the response with optical trackers. Preliminary results demonstrated a vestibular dependence by showing that normal subjects recover from the perturbations in 3–4 steps, while a pilot Labyrinthine Deficient subject required a much longer recovery time.

### ***Artificial Gravity Precursor Studies***

*Kaufman, GD, FO Black, CC Gianna, WH Paloski, and SJ Wood. Otolith and Vertical Canal Contributions to Dynamic Postural Control.*

Kaufman et al. reported that 90-minute hypergravity (1.4g) stimulus (roll plane centripetal acceleration) induces postural and subjective vertical changes in normal and some vestibular deficient subjects.

*Black, FO, SJ Wood, CC Gianna, and WH Paloski. Developing Future Countermeasures for the Detrimental Effects of Space Flight: Role of Otolith Systems & Resolution of Tilt/Translation (poster).*

Black et al. described a new study that will establish the extent to which otolith-mediated tilt and translation responses can be adapted at different stimulus frequencies, and then examine whether subjects can 'dual adapt' to altered sensory environments using the orientation of gravity to provide context.

*Hecht, H and LR Young. Neurovestibular Aspects of Artificial Gravity (poster).*

Hecht and Young described a new multicenter study investigating whether head and body movements during high rate artificial gravity are tolerable and how such artificial gravity can be implemented most efficiently. The study will also investigate methods to minimize the undesirable side-effects of neurovestibular adaptation associated with intermittent artificial gravity.

### ***Clinical Studies***

*Clark, JB and JU Meir. Use of Neurologic Function Rating Scale Following Space Shuttle Flights (poster).*

Clark and Meir reported that a Neurological Function Rating Scale has been designed for clinical assessment of neurological dysfunction associated with space flight. Over 100 crewmembers have now been rated on landing day, and the most severe deficits observed were in gait station and oculomotor disturbances.

## IMPLICATIONS FOR FUTURE RESEARCH

The critical path research plan defines the following five risks (in order of importance) for neuro-vestibular discipline:

1. Disorientation and inability to perform landing, egress, or other physical tasks, especially during/after g-level changes.
2. Impaired neuromuscular coordination and/or strength.
3. Impaired cognitive and/or physical performance due to motion sickness symptoms or treatments, especially during/after g-level changes
4. Vestibular contribution to cardioregulatory dysfunction.
5. Possible chronic impairment of orientation or balance function due to microgravity or radiation.

The current NASA-NSBRI research program addresses each of these risks to some degree, and of the 24 critical questions posed beneath these risks, the current program addresses 21. Thus, the current program appears to have reasonable breadth.

The neuroanatomical results from the peripheral vestibular and cerebellar regions presented at the workshop are extremely important, providing limited anatomical evidence for the long-noted behavioral adaptive responses. Further work should be supported both in tracking the anatomical changes that occur as a function of space flight and in correlating the observed anatomical changes to concomitant behavioral changes.

The vestibulo-autonomic studies presented at the workshop just scratch the surface of the field. Nevertheless, they demonstrate that the vestibular system may exert important influences on both the cardioregulatory system and the motor control system. Further work should be supported in both areas, preferably by cross-disciplinary teams.

The context-specific adaptation studies and related artificial gravity precursor studies are providing important background evidence, in humans, supporting the development of intermittent, rotational artificial gravity as a multi-system countermeasure. NASA-NSBRI should begin funding multi-disciplinary groups to develop and test specific artificial gravity protocols in ground-based studies, and, concomitantly, should begin developing the hardware and infrastructure required for flight testing of an artificial gravity countermeasure.