Functional Responses in Otolith Structures from Micro- to Hyper-Gravity

Invertebrates (behavior/electrophysiology/gene expression)

µG	2 (1.41) G
~15-day: Foton M-2, -3	1-30 day
30-day: BION M-1	

Mice (otoconia structure)

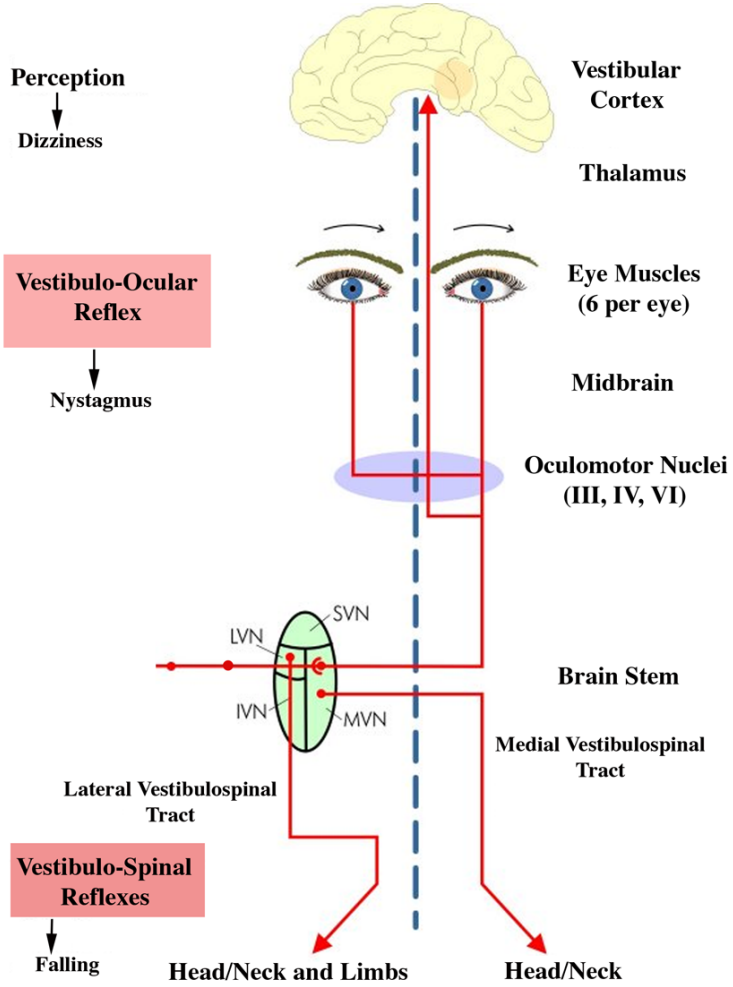
µG	2 (1.41) G
~13-day: STS-133, -135	
90-day MDS: STS-128, -129	90-day MDS: Osaka

Fish (behavior/electrophysiology/synaptic organizaiton)

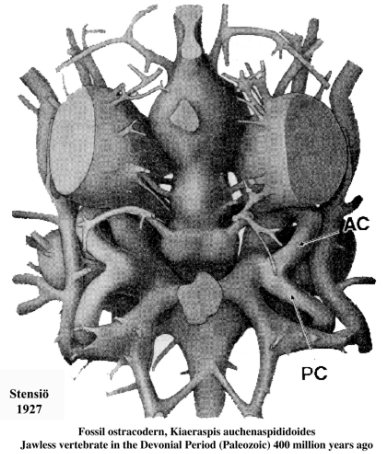
µG	1.5 (1.22G) – 3 (1.73)G
<16-day: STS-90, -95	1-32 day/readaptation

General Concepts Motivating the Study

1) A change in gravity or orientation with respect to gravity has a profound effect on how an organism interacts with its environment.



2) A highly conserved gravito-inertial sensing system has evolved in vertebrates. Otolith organs sense the sum of inertial force due to translation and head tilt re: gravity.



Fossil ostracoderm, Kiaeraspis auchenaspididoides
Jawless vertebrate in the Devonial Period (Paleozoic) 400 million years ago

3) Posture and locomotion are controlled by the neurovestibular system and, if altered, equilibrium and motor performance along the neuraxis will be adversely affected temporarily or even lost without intervention.

Vestibular System: The Inner Ear

- **Semicircular Canals**
  - *Angular Acceleration*
- **Otolith Organs**
  - *Linear Acceleration*

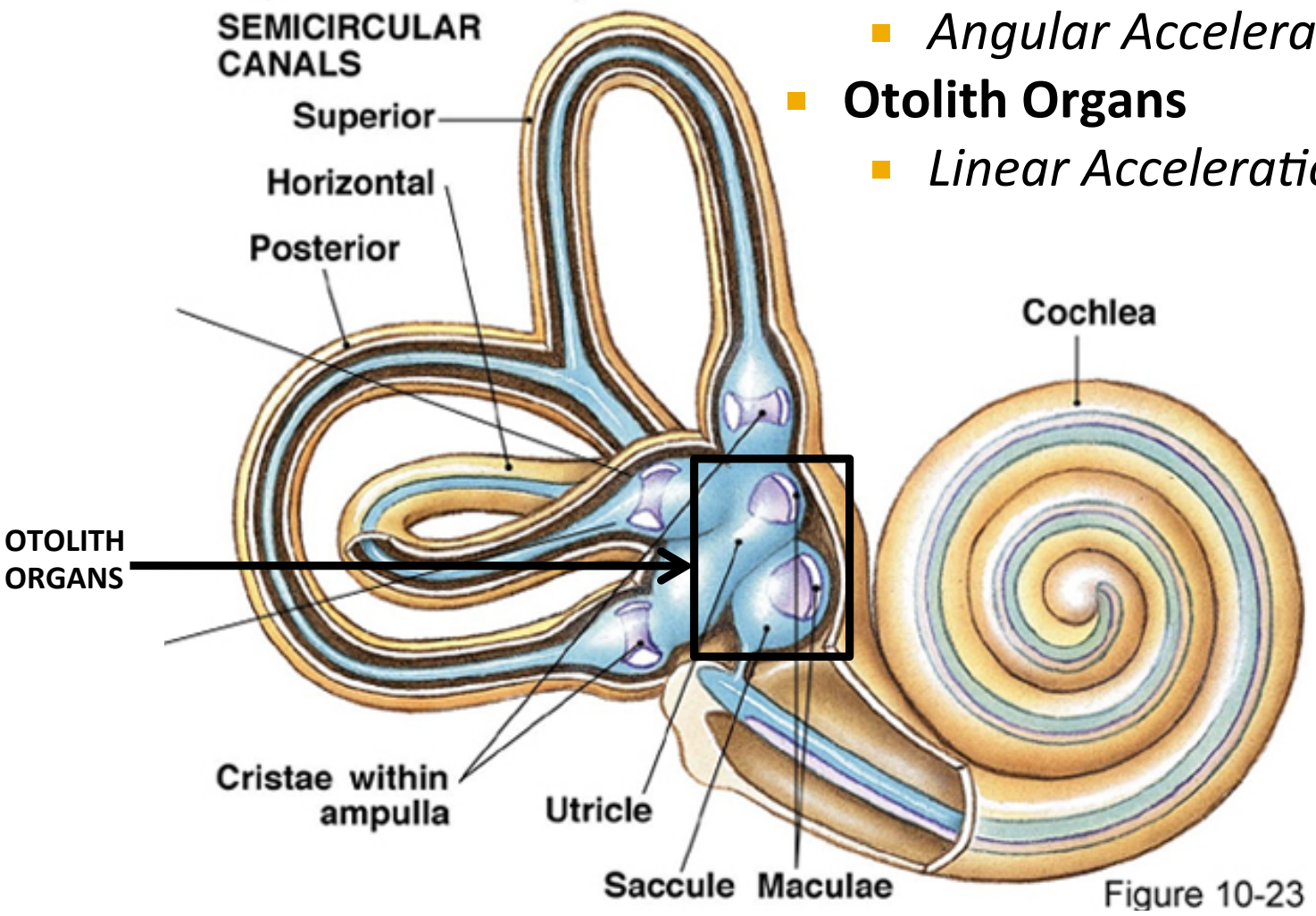
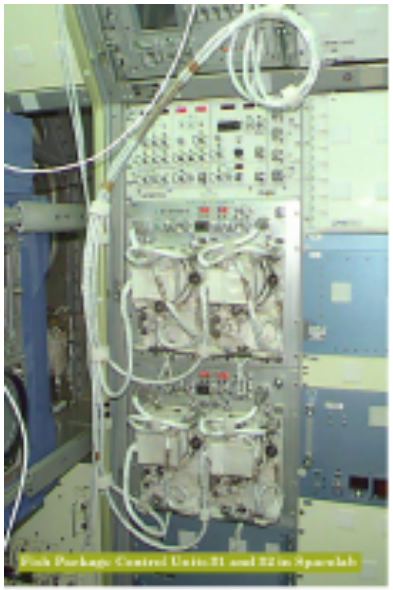
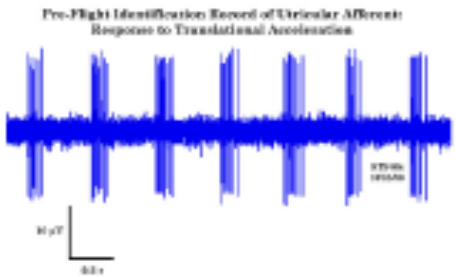


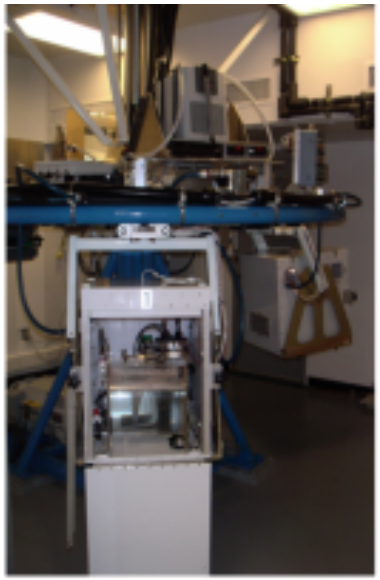
Figure 10-23

Understanding the Fundamental Mechanisms of Neurovestibular Plasticity

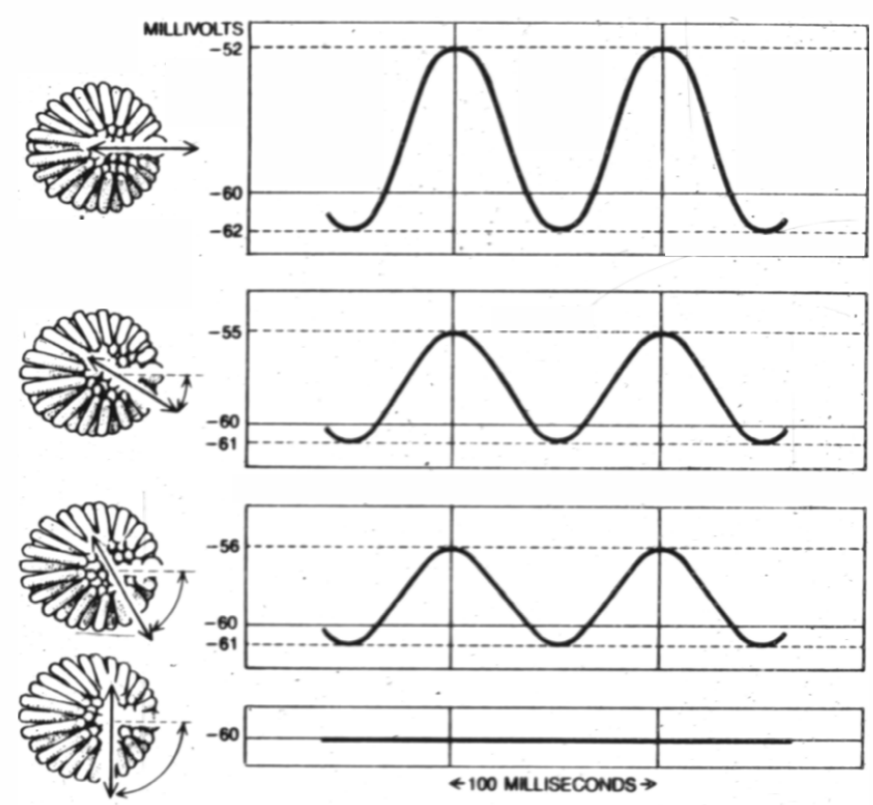
Electrophysiological (and electron microscopy) techniques were used in oyster toadfish to evaluate the firing rate properties of utricular otolith afferents upon return to 1G following a relatively brief exposure to weightlessness aboard the STS-90 (NeuroLab, 15 days) and STS-95 (Endeavor, 8 days) *and* following 1-32 days exposure to 1.73G and re-adaptation to 1G.



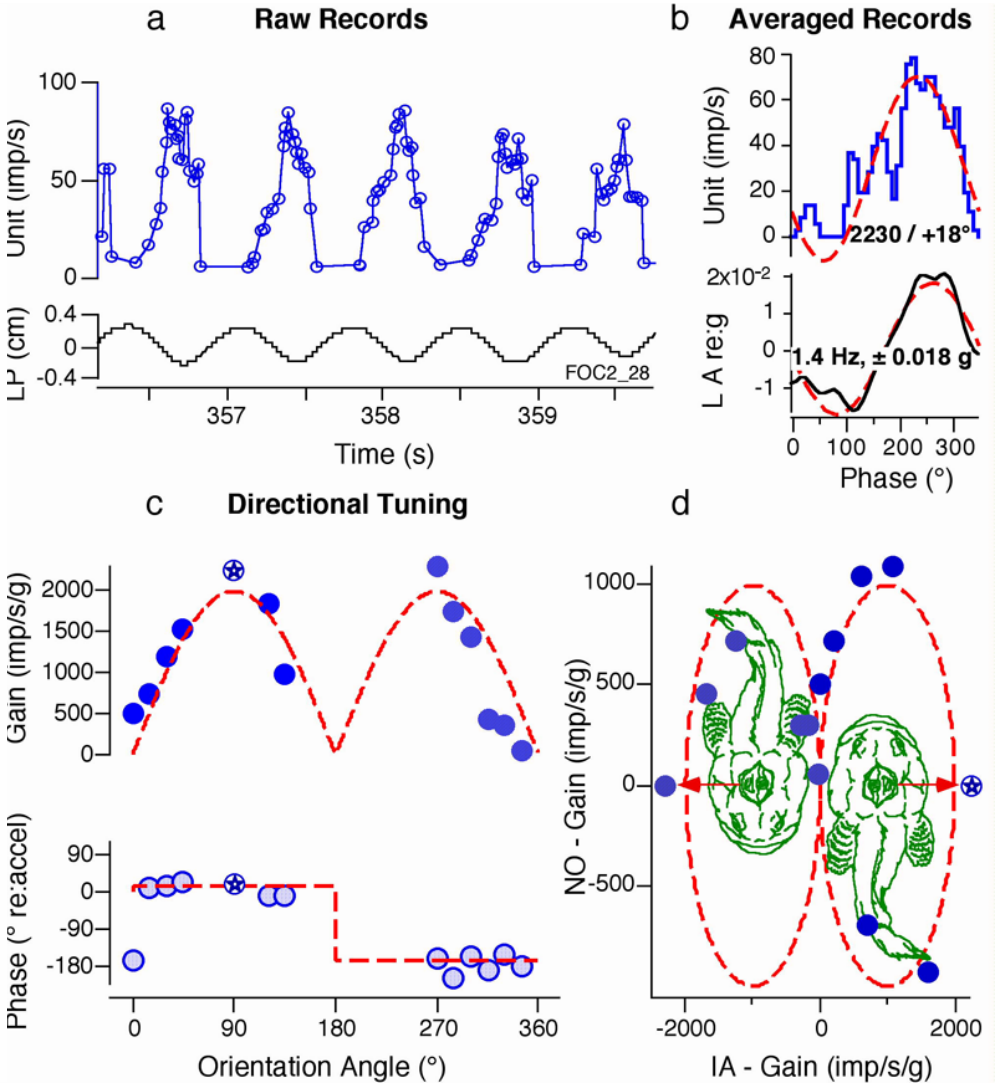




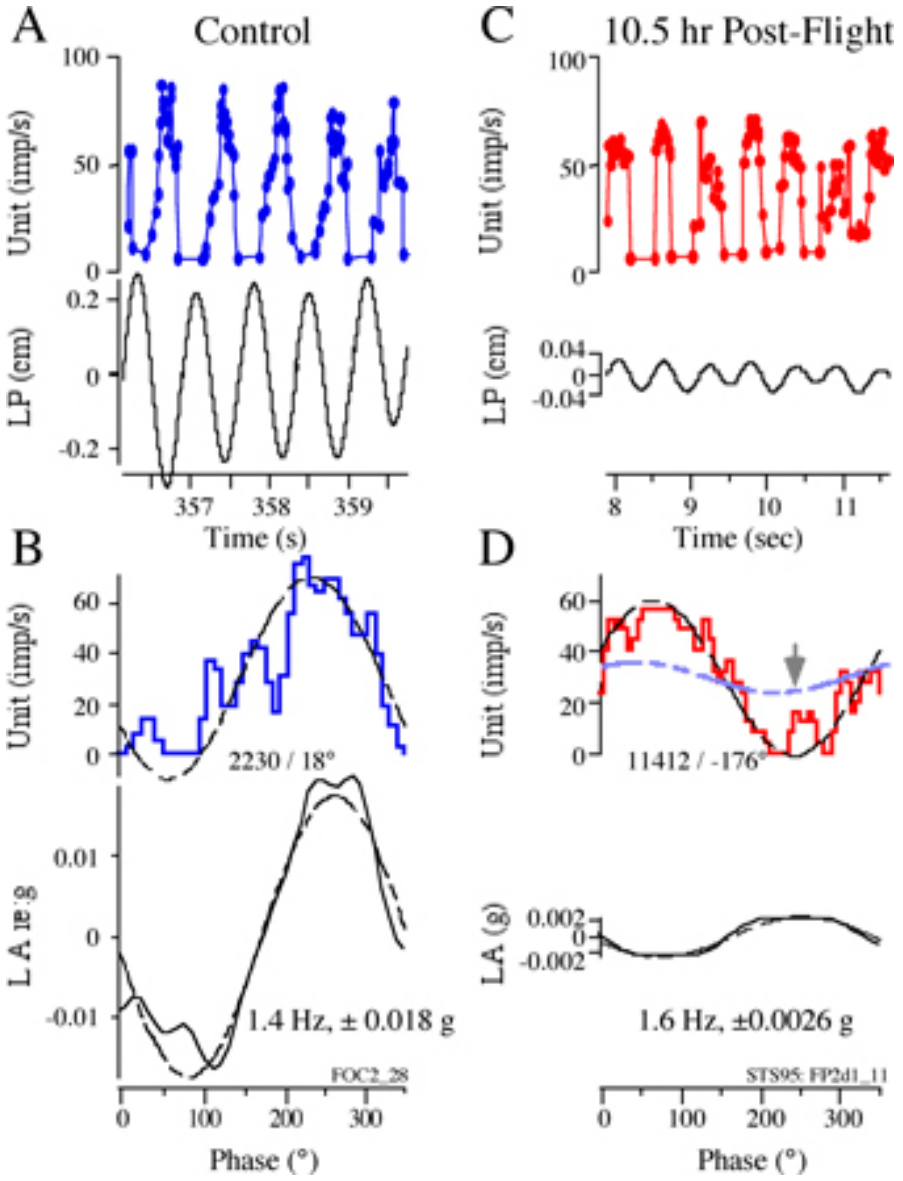
Directional Sensitivity of Hair Cells and Afferents



DIRECTIONAL SENSITIVITY of the hair cell is shown in traces representing recordings made with an electrode inserted into a single receptor from the saccule of the bullfrog while its hair bundle was being moved. The figures are based on experimental records made by Sandra L. Shotwell in the author's laboratory. When the hair cell is in its resting state, its interior has an electric potential 60 millivolts lower than that of the surrounding fluid. If the hair bundle is displaced toward the kinocilium along the axis of bilateral symmetry, the potential difference decreases to −52 millivolts (*top*). If the bundle is displaced away from the kinocilium along the same axis, the difference increases to −62 millivolts. As the direction of displacement diverges from the axis of symmetry the size of the response decreases (*middle panels*). The cell does not respond to displacements along the axis perpendicular to that of symmetry (*bottom*).



Influence of reduced gravity on the vestibular system in vertebrates

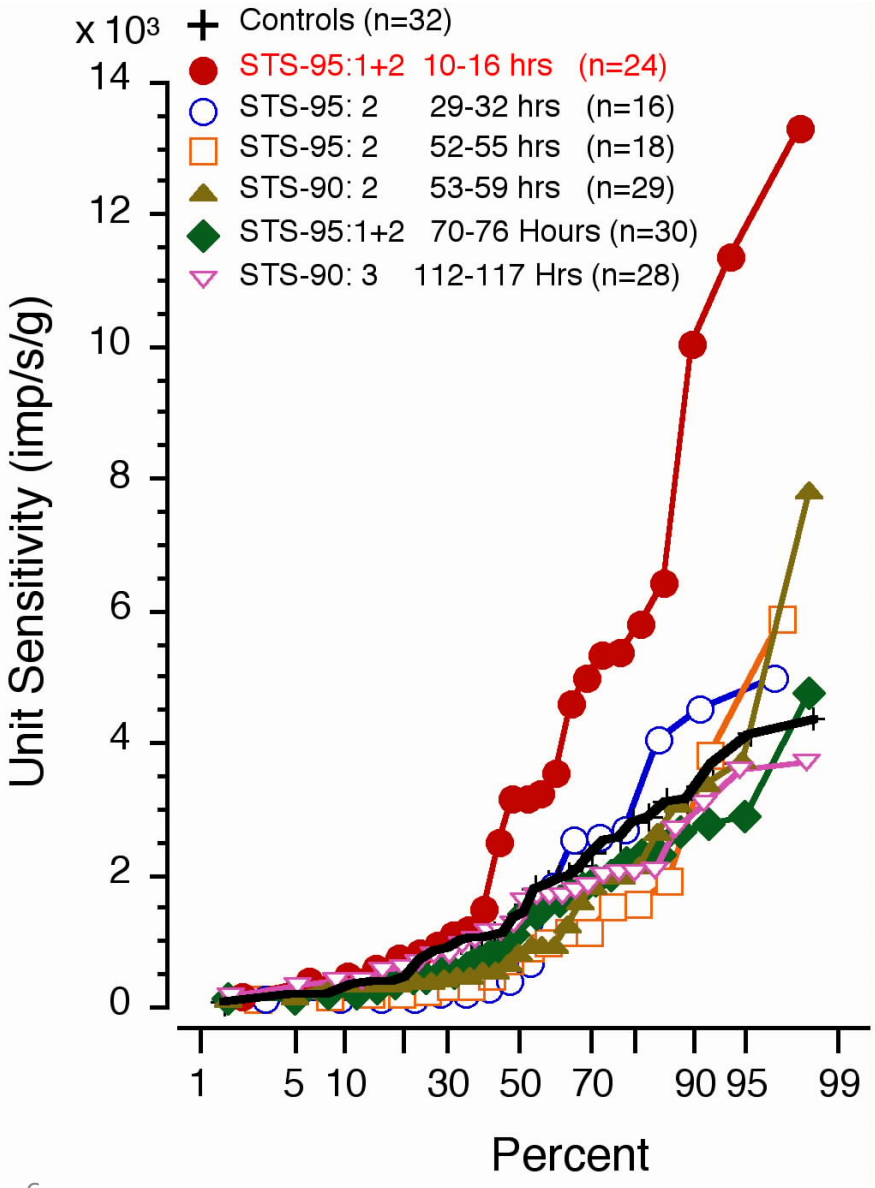


Control (A,B) and postflight (C,D) responses of utricular afferents to inertial accelerations. A,C: Maximum sensitivity (Smax) for cycles at the afferents' preferred orientation. B,D: Averaged response and stimulus (LA re:g). Ordinates in each panel are scaled equally to illustrate the primary finding:

post-flight afferents recorded shortly after return to Earth exhibit a profound hypersensitivity to translational acceleration.

The control response of the afferent shown in A and B is modeled as the dashed curve marked by the arrowhead in the histogram of D.

Influence of Reduced Gravity on the Afferent Sensitivity



Post-flight Afferent Hypersensitivity

Unit sensitivity (in imp/s/g) of individual responses is plotted as a function of percent within each designated group. Groups are formed with respect to time post-flight of STS-90 and STS-95 Orbiters. Note that ~60% of the afferents recorded in the first session (red filled circles) had a significant increase in sensitivity above control (black line).

From: Boyle R, Mensinger AF, Yoshida K, Usui S, Intravaia A, Tricas T, and Highstein SM. (2001) Neural readaptation to 1G following return from space. *J. Neurophysiol.* 86: 2118-2122.

STS-90 and -95: Main Findings

•Responses of utricular afferents to applied translational accelerations were recorded in 4 fish sequentially for 5 days following two STS flights. ***Within the first day after landing, the magnitude of response was on average three-times greater than controls.*** The reduced gravitational acceleration in orbit apparently resulted in an up-regulation of the sensitivity of utricular afferents.

•By ~ 30 hours post-landing, responses were statistically similar to control. The time course of return to normal approximately parallels the decrease in vestibular disorientation in astronauts following return from space.

•The data suggest that neural adaptive mechanisms, likely involving structural reorganization of the hair cell-afferent synapse (Ross 1993), will be set into motion as astronauts transition between gravity states.

•Although we attempted to characterize the utricular afferents during the entire mission, particularly during the first 3-4 days when astronauts experience disorientation, we were unsuccessful.

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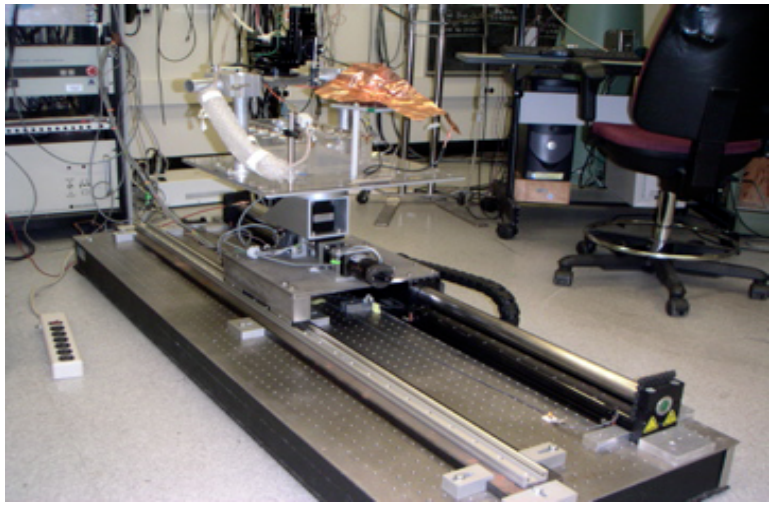
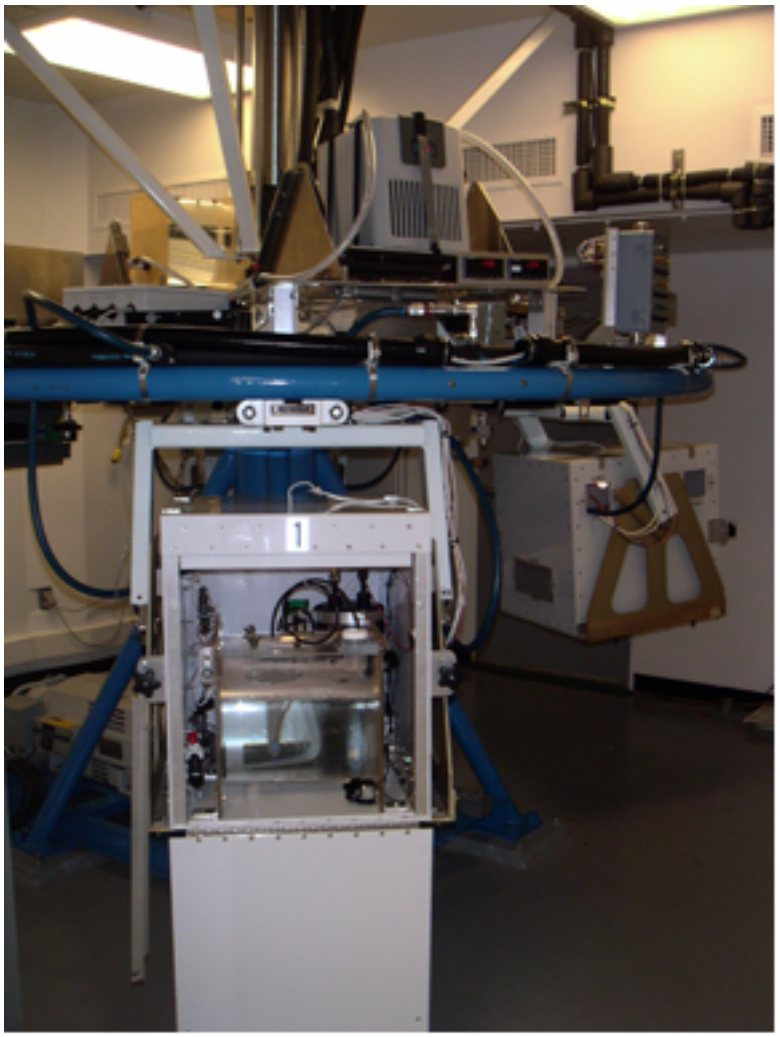
Influence of Increased Gravity and Duration of Exposure on the Vestibular System

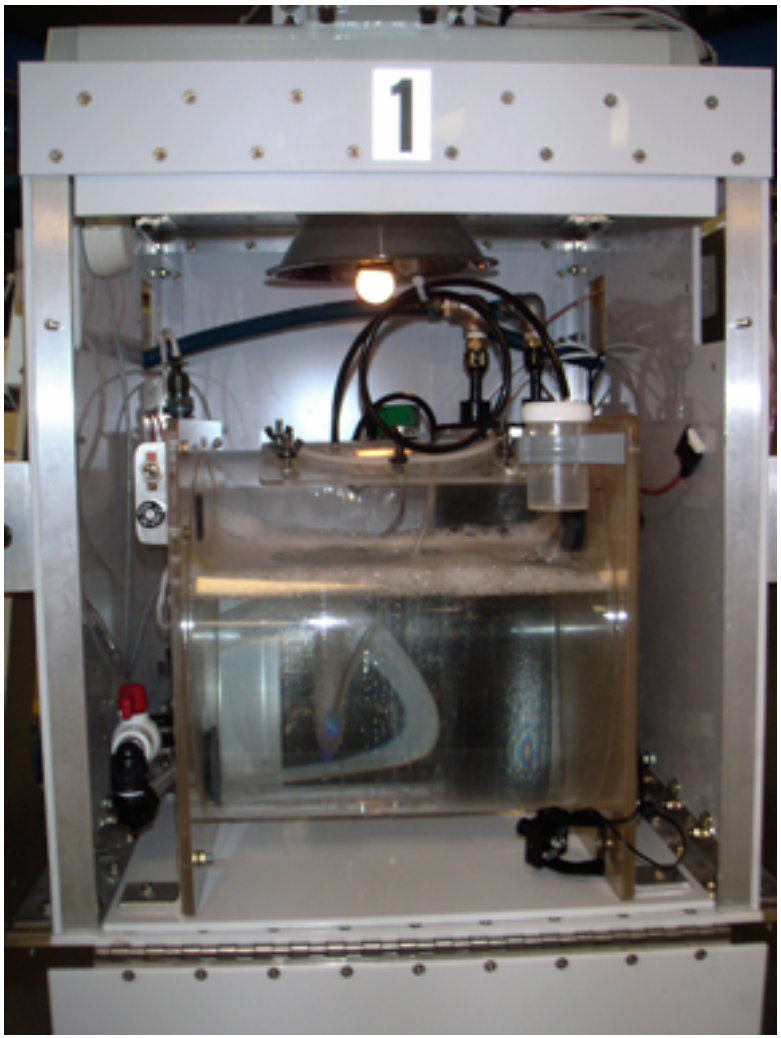
The **Hyper-G** study is based on the following hypothesis: gravito-inertial sensitivity of otolith afferents is altered as a result of the animal's exposure to hyper-G conditions well as µG. It is reasoned that the transition from 1G to hyper-G will decrease afferent sensitivity (impulses per sec/g), and the transition from hyper-G back to 1G will increase it (back to normal levels). *Thus, the transition from hyper-G to normal gravity may serve as an imitator of neurovestibular sequelae to µG.*



Testing Apparatus: servo-controlled using WaveMetrics Igor scripts to Galil controller to drive linear acceleration (1.5m), yaw rotation (static displacement and sinusoids), and tilt (pitch to roll) motion profiles. Because of the high sensitivity and to avoid impulse rate saturation, a common linear acceleration test is ±0.03-0.05g at 1-2 Hz.

Planned International Space Station (ISS) 1.22 m radius centrifuge at Ames Research Center

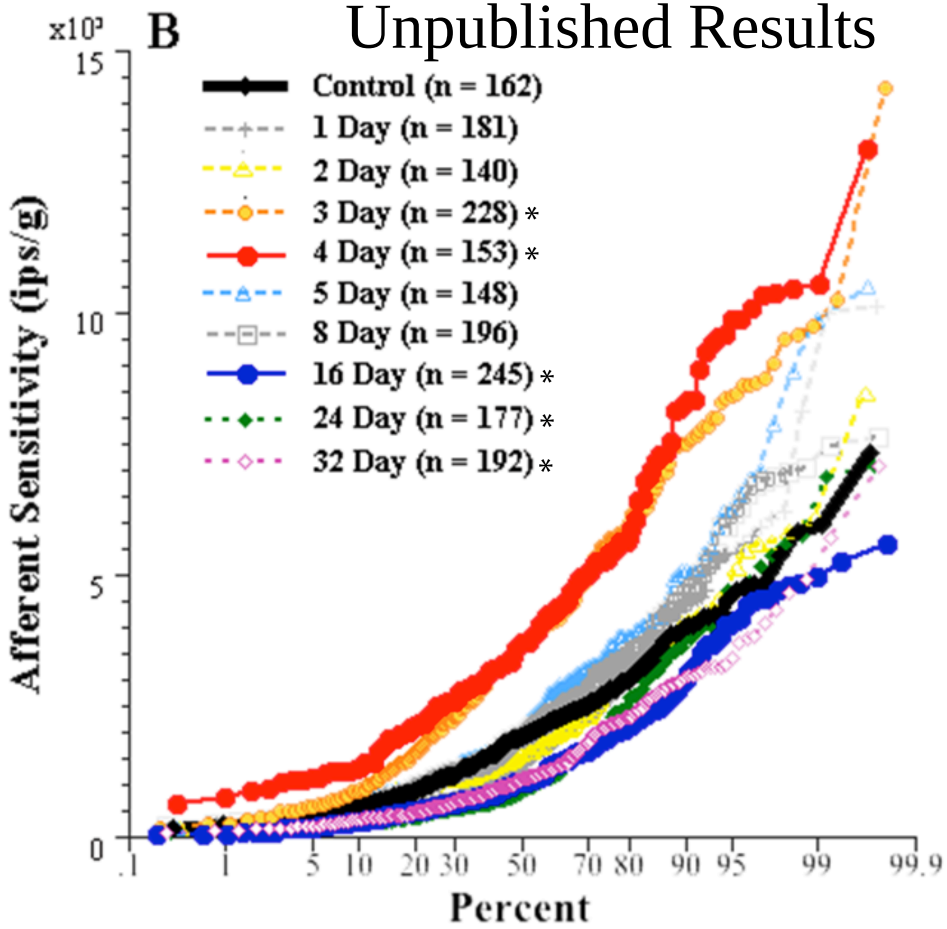


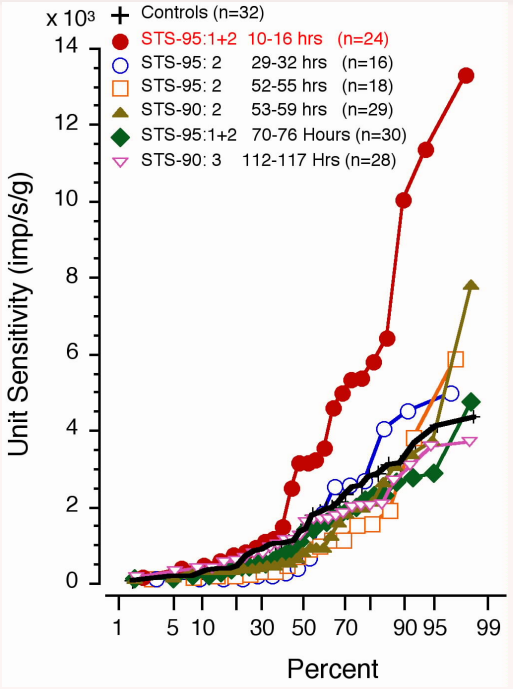


Radius: 1.22m Payload: 87 kg/habitat

Influence of Increased Gravity and Duration of Exposure on Afferent Sensitivity

Unpublished Results



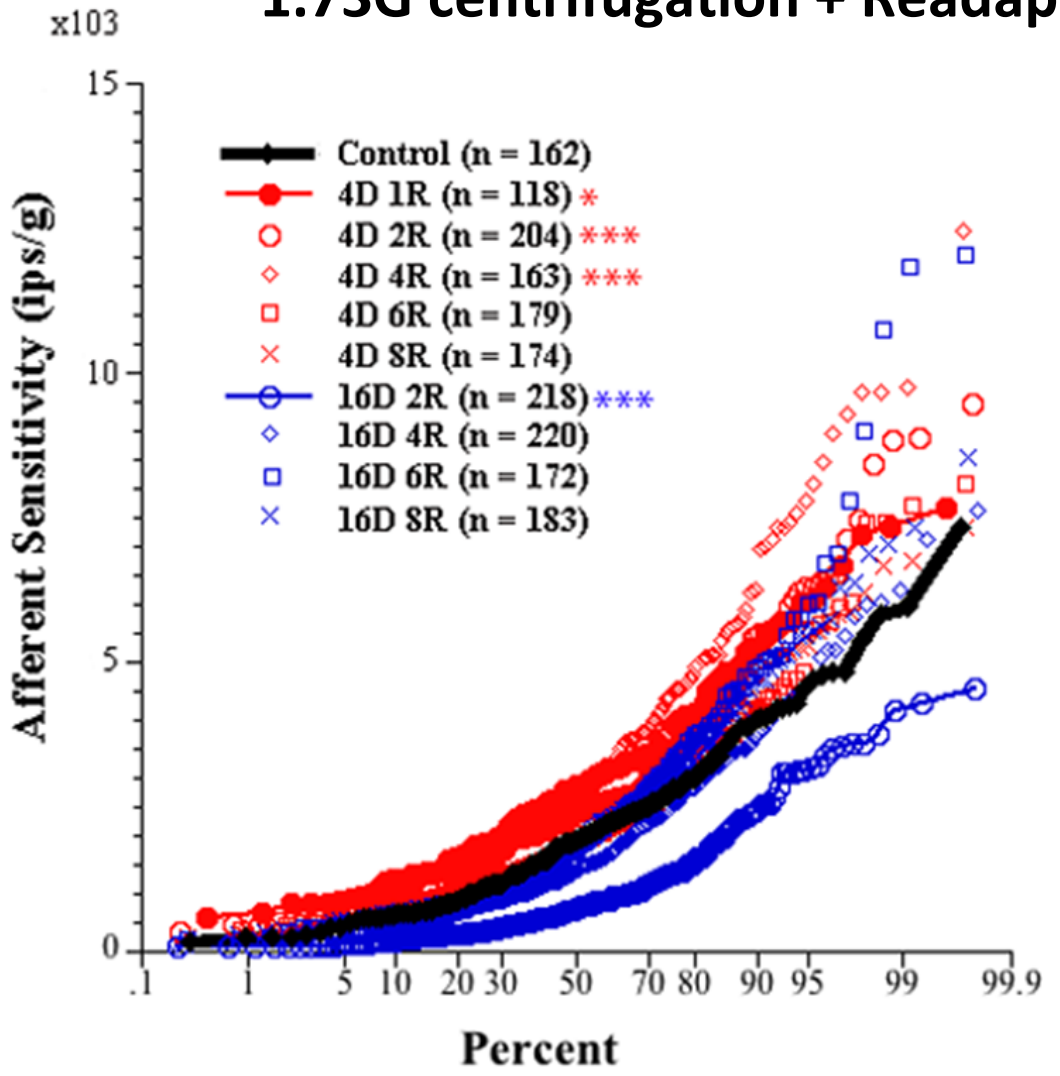


Post-flight afferents recorded after return to Earth exhibit a profound hypersensitivity to translational accelerations.

Significant elevation (*) of Smax at 3- and 4-Day was observed, followed by a significant decrease (*) at 16-, 24-, and 32-Day. *It is possible that the altered gravity (AG) initiates first* a large gain increase in response to a challenge, any AG challenge. In this scenario we would expect to observe a change in response sensitivity in the early stages of µG exposure as well. Regrettably, those data are lacking.

Influence of Increased Gravity and Duration of Exposure on Afferent Sensitivity

1.73G centrifugation + Readaption to 1G



Following 4- and 16-day exposure to √(1+2) = √3 = 1.73G centrifugation, about ***2-4 days of recovery*** at 1G are necessary for the otolith afferents to return as a population to normal levels of response sensitivity.

Unpublished Results

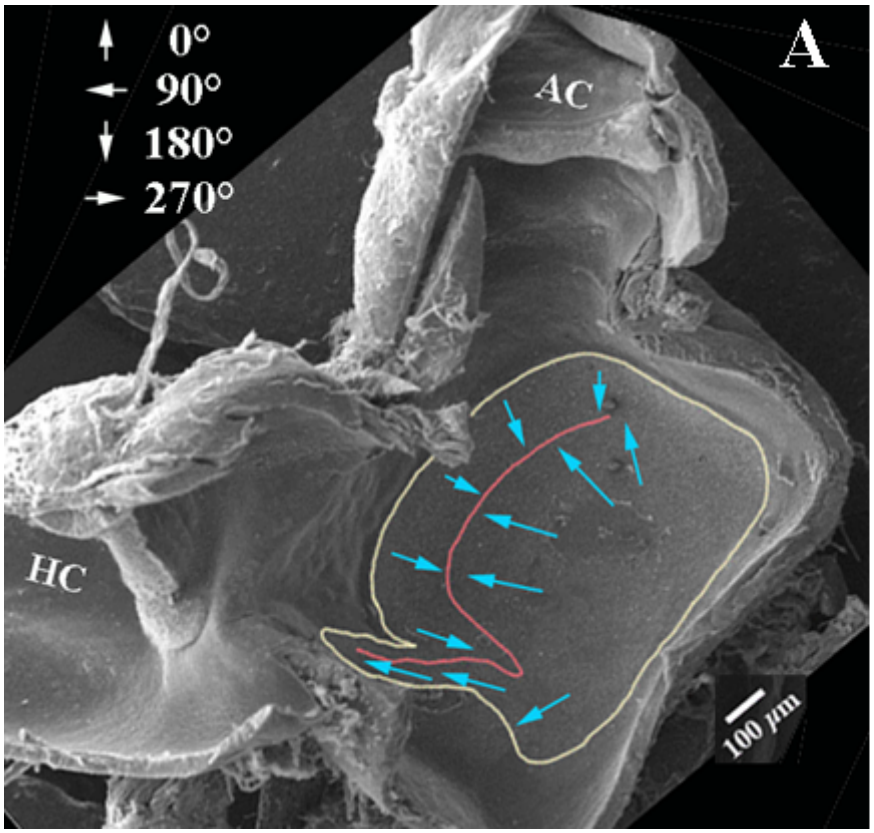
Unpublished Results

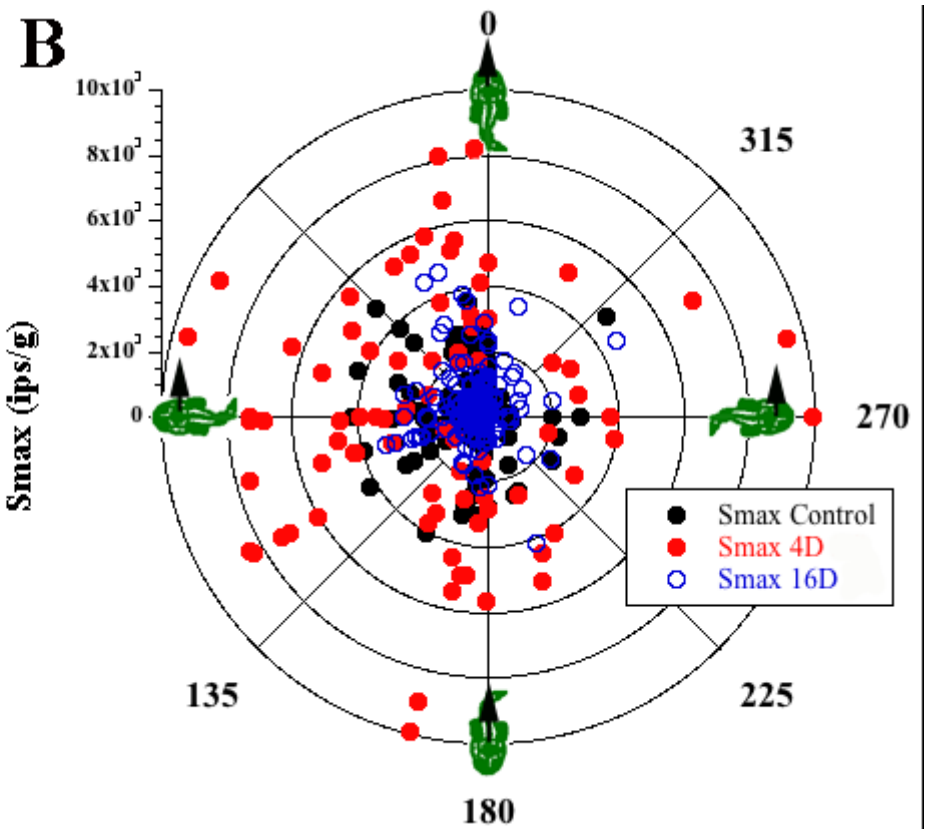
Group	UtrN =	Smax (ips/g)	Smin/Smax	Head Angle (°)	IR (ips/cycle)	HCN N=	IR (ips/cycle)
1D 1.73G	181	1981 ±1769	0.09 ±0.14 (66)	87 ±76	43 ±24	50	40 ±20
2D 1.73G	140	2042 ±1435	0.08 ±0.13 (55)	73 ±100	29 ±18**	86	40 ±20
3D 1.73G	228	3935 ±2466***	0.09 ±0.13 (88)	72 ±83	40 ±23	53	41 ±25
4D 1.73G	153	4241 ±2553***	0.09 ±0.13 (112)	115 ±90	39 ±22	70	39 ±18
5D 1.73G	148	2599 ±1920	0.1 ±0.128 (44)	90 ±76	27 ±18***	30	40 ±23
8D 1.73G	196	2326 ±1654	0.1 ±0.1 (70)	81 ±97	26 ±15***	89	39 ±21
16D 1.73G	245	1398 ±1154***	0.11 ±0.13 (119)	87 ±78	31 ±18**	133	40 ±23
24D 1.73G	177	1495 ±1462**	0.09 ±0.11 (78)	96 ±98	24 ±16***	49	39 ±22
32D 1.73G	192	1443 ±1154**	0.1 ±0.11 (84)	77 ±80	24 ±17***	44	40 ±18
4D 1Rec	118	2751 ±1581*	0.01 ±0.16 (58)	69 ±82	31 ±15**	70	41 ±18
4D 2Rec	204	3034 ±1703***	0.1 ±0.13 (78)	77 ±60	43 ±21	84	38 ±23
4D 4Rec	163	3214 ±2315***	0.09 ±0.1 (63)	100 ±104	42 ±23	40	41 ±12
4D 6Rec	179	2228 ±1482	0.08 ±0.07 (69)	68 ±55	36 ±19	34	40 ±23
4D 8Rec	174	2347 ±1569	0.09 ±0.09 (74)	65 ±67	43 ±24	42	42 ±21
16D 2Rec	218	1033 ±941***	0.08 ±0.14 (90)	64 ±59	42 ±28	75	40 ±23
16D 4Rec	230	1826 ±1418	0.09 ±0.12 (101)	72 ±83	43 ±25	73	42 ±24
16D 6Rec	172	2386 ±2062	0.095 ±0.14 (67)	80 ±63	42 ±26	56	38 ±19
16D 8Rec	183	2244 ±1613	0.09 ±0.13 (74)	70 ±78	43 ±22	44	41 ±21
4D 1.22G	184	3274 ±2113***	0.1 ±0.12 (65)	70 ±92	43 ±21	53	39 ±16
16D 1.22G	183	1940 ±1430	0.09 ±0.13 (45)	66 ±87	39 ±21	44	41 ±24
4D OCC	226	2291 ±1378	0.1 ±0.13 (86)	68 ±53	37 ±16	90	41 ±16
16D OCC	177	2252 ±1597	0.1 ±0.1 (52)	79 ±55	36 ±17	72	38 ±24
Control	**162**	**2103 ±1314**	**0.085 ±0.14 (81)**	**95 ±82**	**40 ±19**	**58**	41 ±21

* p<0.05
** p<0.005
***p<0.0001

Total # fish for this table 36 expt'al + 12 control + 8 OCC + 8 1.22g + 9 re-adapt= 73 fish and 4233 afferents in table

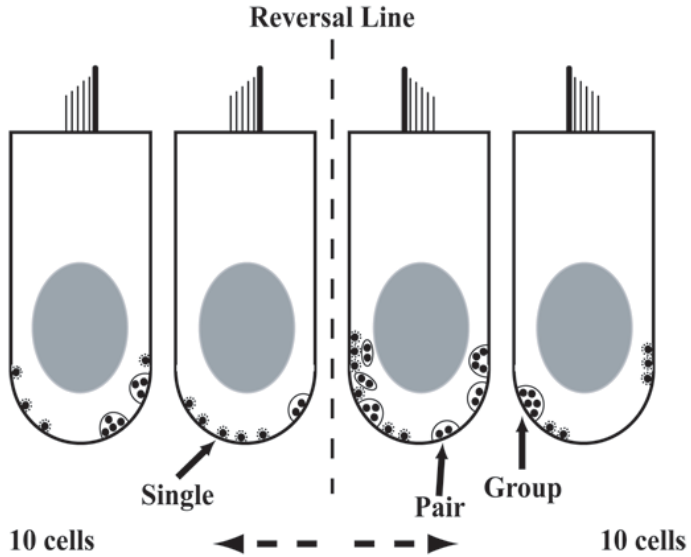
Afferent Directional Selectivity



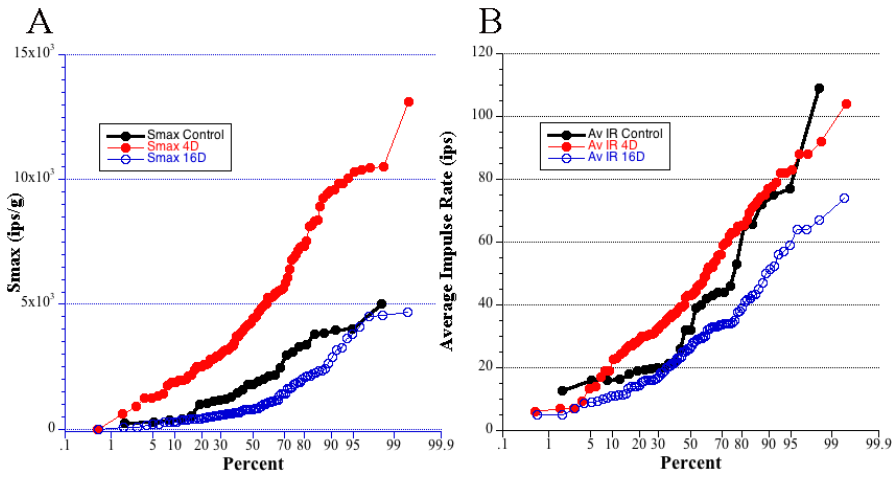


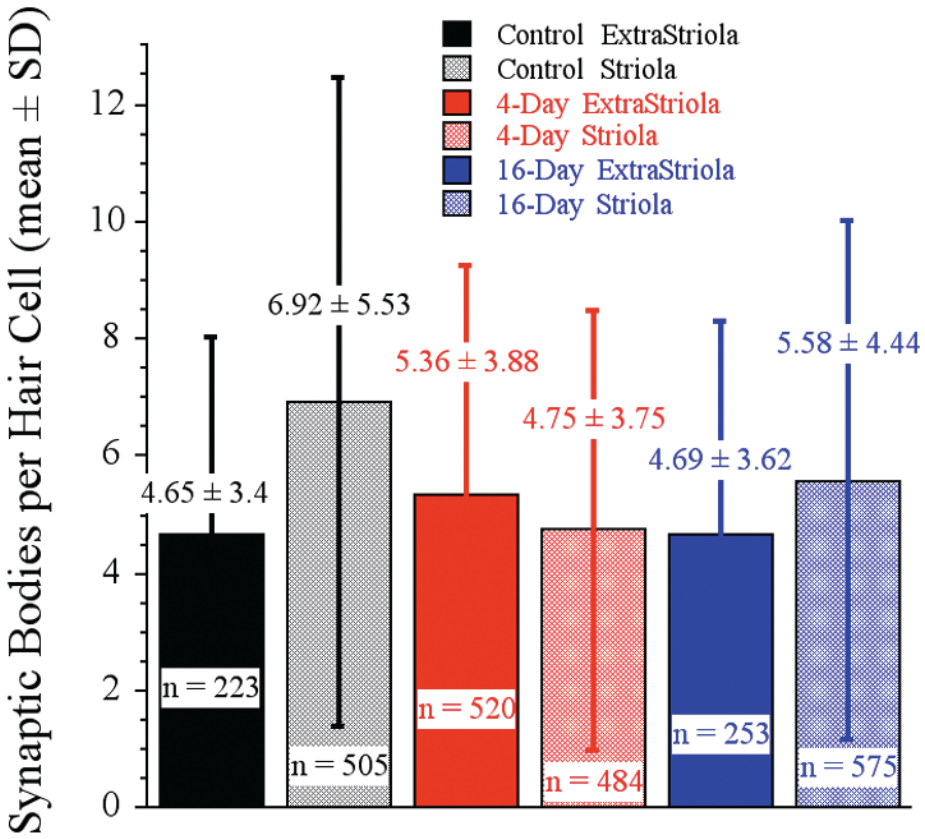
Unpublished Results

Are the addition or subtraction of synaptic bodies in utricular hair cells responsible for the observed afferent sensitivity following centrifugation?



We selected 2 animals in control, 4D, and 16D groups and counted synaptic bodies in 2 locations of the macula using serial reconstructions from transmission electron micrographs. Note the physiological separation of the controls. NO significant differences were found.





Unpublished Results

Summary: Influence of Altered Gravity on the Peripheral Vestibular System in Vertebrates

•Otolith afferents recorded after return to Earth exhibited a profound *hypersensitivity* to translational accelerations, and recovery to normal level was within 1-2 days. It is reasonable to suggest that astronaut behavior following a short-term exposure to μG reflects the physiological changes occurring in the otolith structures.

Unpublished Results

•A biphasic pattern in response to hyper-G is observed: an *initial hypersensitivity* (3- to 4-day), similar to that observed in otolith afferents upon return to 1G, followed by a transition through normal sensitivity to a significant *hyposensitivity* at 16- to 32-day exposure. Return to control values following 4- and 16-day exposure to 1.73G is ~4-8 days. The initial hypersensitivity might reflect the more common transient symptoms experienced by astronauts in the early stages of the mission.

Summary: Influence of Altered Gravity on the Peripheral Vestibular System in Vertebrates

•*Animal behavior* within the first day post-flight and within the first days of hyper-G was noted: a hyper-excitable state and a reluctance to move. This initial behavior to *altered gravity* (AG) likely reflects the hypersensitivity of otolith nerve afferents. *It is possible* that AG *initiates first* a large gain increase in response to a challenge, any AG challenge. Using animal behavior as an indicator of the underlying otolith afferent physiology, intermittent or partial AG exposure on ISS might be applied to query neurovestibular changes and validated parameters as potential countermeasure protocols.

Unpublished Results