Fiscal Year:	FY 2014	**Task Last Updated:**	FY 08/26/2014
PI Name:	Boyle, Richard Ph.D.		
Project Title:	Inner Ear Otoconia Response in Mice to Micro- and Hyper-gravity		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Sensorimotor**:Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	94035-1000	**Congressional District:**	18
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2011 Crew Health NNJ11ZSA002NA
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No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA ARC
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Flight Program:			
Flight Assignment:	NOTE: Extended to 3/31/2014 (original end date was 6/30/2013) per A. Chu/ARC (Ed., 6/11/13)		
Key Personnel Changes/Previous PI:			
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	Does exposure to long-duration spaceflight lead to neural structural alterations and does this remodeling impact cognitive and functional performance? This knowledge gap (SM26) recognizes an inherent risk to crew health and performance due to neural structural plasticity associated with space flight. Otoconia crystals of the mammalian inner ear otolith sensory organs are critical for spatial orientation and balance. Because of their normal biomineralization and their density is related to neural sensitivity, exposure to long-duration spaceflight puts them at risk to structural remodeling. A widely considered mechanism by which the nervous system responds to a change in gravity load is a change in the weight-lending otoconia. When subjected to weightlessness, it is argued the organism counters the loss of gravity load by increasing calcium carbonate production, thereby seen as a means to increase the "system gain". Our hypothesis is: weightlessness over a significant period of time triggers a compensatory mechanism that leads to a constructive process		

Task Description:	of ion deposition and an increase of otoconia mass. Upon entry to a novel gravity environment and later return to Earth, this response is maladaptive and will have a severely negative impact on cognitive and functional performance of the crew during the mission and on health and wellness at home. Although not mutually exclusive, we also hypothesize that long-duration hypergravity exposure leads to an ablative process and loss of otoconia mass. On Earth the clinical syndrome of canalithiasis, the most common single cause of vertigo, is now clearly biomechanical in origin and occurs when otoconia or fragments from them are displaced from their normal location. Despite this significant morbidity, the potential exists for structural remodeling of otoconia by the intensity and duration of gravity loading to which the animal is exposed? To address this risk we have one specific aim, namely to specify the structural integrity of otoconia as a result of short- and long-duration exposures to altered gravity conditions. Until recently, mammalian studies were confined to space missions and ground-based centrifugation studies of relatively short duration, and as a result studies have reached mixed conclusions. The Mouse Drawer System (MDS) housed mice on the International Space Station (ISS) for 91 days, roughly 20% of the lifespan of a mouse in the wild. Preliminary results of inner ears of MDS flight mice showed a dramatic alteration of symmetry and topographical surface features of otoconia; controls were normal in appearance. Subsequent studies have acquired otoconia samples from: 1) equivalent mouse models of MDS mission to 2G centrifugation and hindlimb unloading for 91 days in two separate series; and 2) inner ear samples of mice flown on the 13-day STS-133 and -135 missions. Preliminary results of inner ears of 2G mice also showed a dramatic alteration in topographical features of otoconia, but in the opposite sense in support of our hypothesis. The proposed research is a one year ground-based study from existing tissues and addresses fundamental mechanisms of neural compensation that directly effect crew health and performance during the exploration missions and on return to Earth. We will apply scanning and transmission electron microscopy and microstructural-crystallographic techniques to evaluate the possible mechanisms of otoconia restructuring in response to gravity loading. We specifically seek to answer the following questions: are there structural changes in otoconia as a result of experimental altered gravity conditions? If so, is the change due to a constructive or destructive process? And, is the process dependent on length of exposure to altered gravity loading? It is anticipated that the study will produce both a path toward quantification of a crew health and performance risk and provide the basis for valid ground-based studies for countermeasure development.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Inner ear structures have adaptive processes to regulate their function. Because of low endolymphatic levels of calcium and carbonate ions, efficient concentrating mechanisms mediated predominantly by glycoproteins are required for crystal nucleation and growth (Thalmann I, Hughes I, Tong BD, Ornitz DM, and Thalmann R. 2006. Microscale analysis of proteins in inner ear tissues and fluids with emphasis on endolymphatic sac, otoconia, and organ of Corti. Electrophoresis 27: 1598-1608). Otoconia function is not fixed: the shell can turn over (Thalmann R, Ignatova E, Kachar B, Ornitz DM, and Thalmann I. 2001. Development and maintenance of otoconia: biochemical considerations. Ann NY Acad Sci 942: 162-178), and they slowly and progressively degenerate in aging, resulting in loss of balance and falls in elderly patients. Clinical syndrome of canalithiasis (Epley JM. 1994. Positional vertigo related to semicircular canalithiasis. Otolaryngology Head and Neck Surgery 112: 154-161), the most common single cause of vertigo, is biomechanical in origin and occurs when otoconia fragments are displaced from their normal location. Despite the significant morbidity, little is known about the structural processes involved in otoconia maintenance, and possible pathology, from long-term weightlessness.
Task Progress:	The overall findings of this study provide a more comprehensive understanding of the structural integrity of otoconia in response to adverse consequences of weightlessness, provide a time frame in which structural changes are expected, and identify possible fundamental mechanism(s) of plasticity used by the nervous system. We are still pursuing other techniques in the short term to enhance our imaging of the otoconia in the different mice. Together with existing data our current findings indicate that the initial response to weightlessness is likely a change in synaptic organization due to unweighting of the otoconia mass and a change in mechanical linkage between otoconia and hair cell stereocilia, and the influence on otoconia integrity is relatively minor. The initial responses to microgravity are rapid and are likely confined to the hair cells as evident by an increase in synaptic bodies and a hypersensitivity of the supplying vestibular nerve afferents. However, in response to prolonged missions a compensatory structural change in otoconia is induced through a constructive process of $CaCO_3$ deposition; in gravity altered environments in the opposite sense, namely gravity loading via centrifugation, a compensatory structural change in otoconia is induced through a destructive process of $CaCO_3$ ablation. The electrophysiological results of a current study in the laboratory support the present findings. In animals exposed to variable duration hypergravity (3G centrifugation) vestibular nerve afferents show a biphasic response: initially over the first 3-4 days the afferent are hypersensitivity to head accelerations suggesting a rapid change in synaptic organization, followed by a severe hyposensitivity when the 3G centrifugation continues to extended durations suggesting a possible remodeling of the otoconia. If structural changes do indeed occur, as our results suggest, these data will establish the basis of crew monitoring protocols, quantitative diagnostic tests of inner ear health and biomechanical function during flight and, more importantly, within a gravity environment on the mission and at home for early detection of pathology, and development of countermeasures to mitigate long-term health risks. However, caution is still needed in the final interpretation, because the samples were collected in tissue sharing programs. Defining the mechanisms underlying these observed structural changes of the otoconia in altered gravity environments requires more experimental manipulations of parameters that were not possible in the present confines of the programs, such as simply having detailed blood chemistry profiles in the different mice.
Bibliography Type:	Description: (Last Updated: 09/17/2021)
Abstracts for Journals and Proceedings	Boyle R, Popova Y, Varelas J. "Functional and structural changes in otolith structures from micro- to hyper-gravity in vertebrates." 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. http://www.hou.usra.edu/meetings/hrp2014/pdf/3062.pdf , Feb-2014
Abstracts for Journals and Proceedings	Boyle R, Popova Y, Varelas J. "Functional and structural responses in otolith structures from micro- to hyper-gravity in vertebrates." Presented at International Workshop on Research and Operational Considerations for Artificial Gravity Countermeasures, Moffett Field, CA, Feb 19-20, 2014. International Workshop on Research and Operational Considerations for Artificial Gravity Countermeasures, Moffett Field, CA, Feb 19-20, 2014. , Feb-2014

Articles in Peer-reviewed Journals	Popova Y, Boyle R. "Neural response in vestibular organ of Helix aspersa to centrifugation and re-adaptation to normal gravity." J Comp Physiol A Neuroethol Sens Neural Behav Physiol. 2015 Jul;201(7):717-29. Epub 2015 Mar 24. http://dx.doi.org/10.1007/s00359-015-1003-x ; PubMed PMID: 25801308 , Jul-2015
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