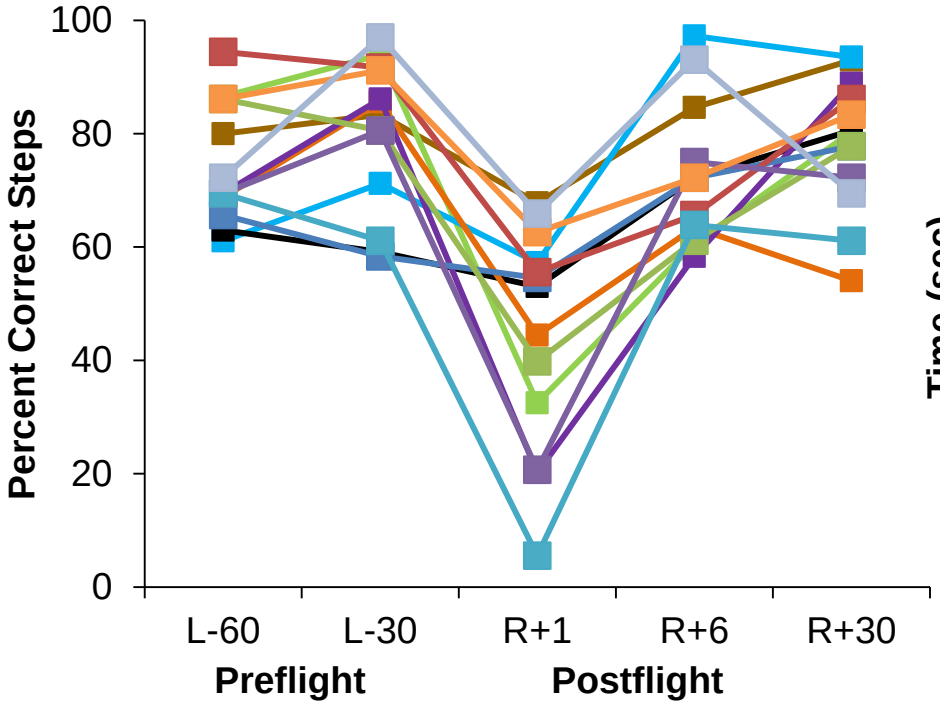
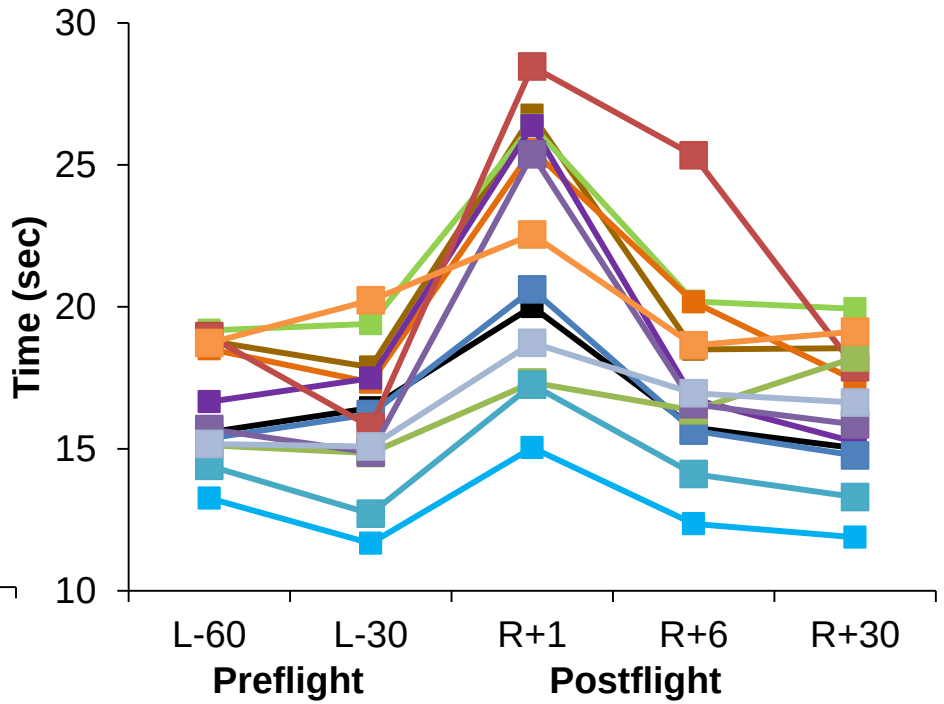
Behavioral, Brain Imaging, and Genomic Measures To Predict Functional Outcomes After Bed Rest And Spaceflight

Mulavara A, Peters B, De Dios Y, Gadd N, Caldwell E, Watson C, Oddsson L, Kreutzberg G, Zanello S, Clark T, Waddington G, Oman C, Cohen H, Wood S, Seidler R, Reschke M, Bloomberg J.

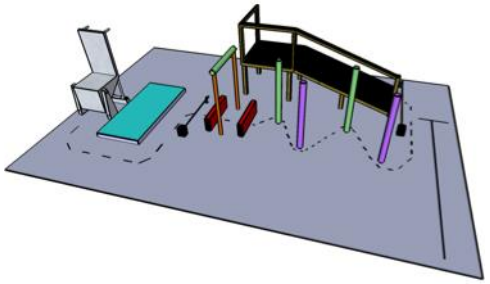
Astronauts show variability in adaptive responses





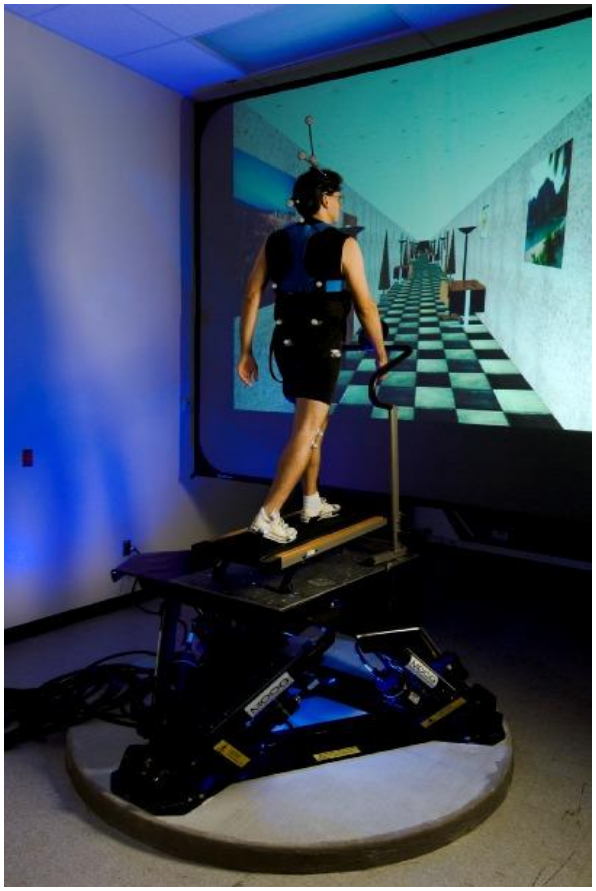
Tandem Walk Test

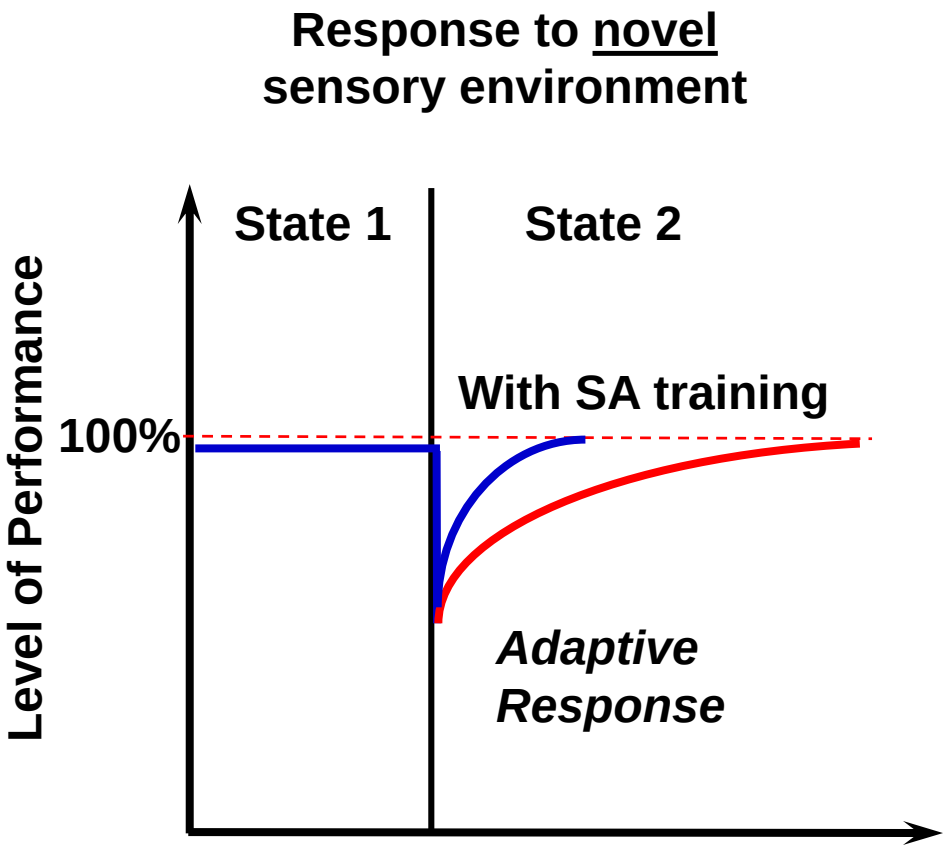
After long duration space flight



Seat Egress and Walk Test

Sensorimotor Adaptability Training





- ***Training that provides multiple sensory challenges enhances ability to adapt to novel sensory environments***
- ***Promotes "learning to learn"***

Study Objectives

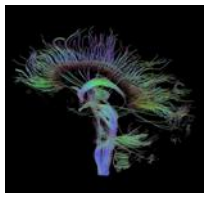
1. Develop a set of predictive measures capable of identifying individual differences in sensorimotor adaptability.

2. Use this information to design sensorimotor adaptability training countermeasures that are customized for each crewmember’s individual sensory bias and adaptive capacity.

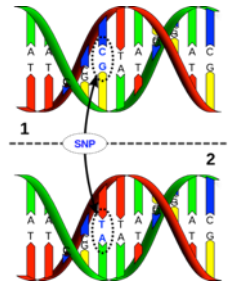
Sensorimotor Predictors Retrospective Study

Prospective Data
(1 session ~ 3 Hours)

Behavioral Metrics
- Sensory utilization
- Motor Learning



Brain Structural and Functional Metrics



Genomic Metrics

Retrospective Data

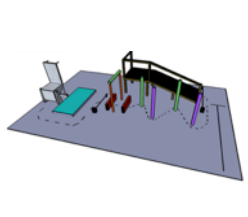
Treatments

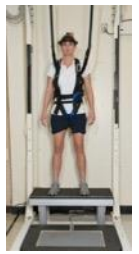
Short/long duration space flight

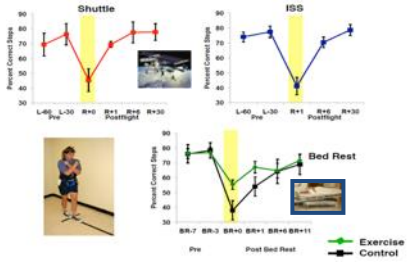
22 ISS (13 FTT, 3 FT, 6 USOS PFT)
7 Shuttle

70 day, 6° Head down tilt bed rest

10 Controls





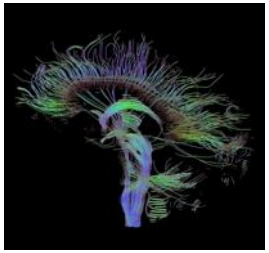


Retrospective FTT/FT data from completed missions

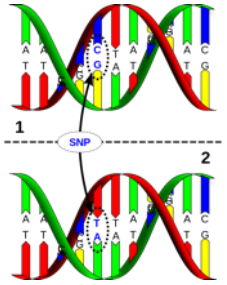
Ground Based Study (N = 16 normal subjects): Do these metrics predict adaptive locomotor performance in a sensory discordant environment?

Predictors

Behavioral Metrics
- Visual Dependency
- Proprioceptive Function
- Balance Control
- Motor Learning



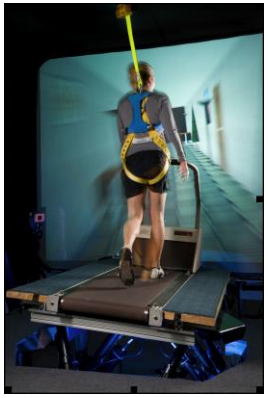
Brain Structural and Functional Metrics

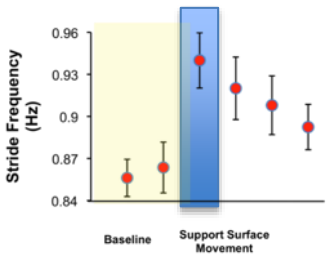


Genomic Metrics

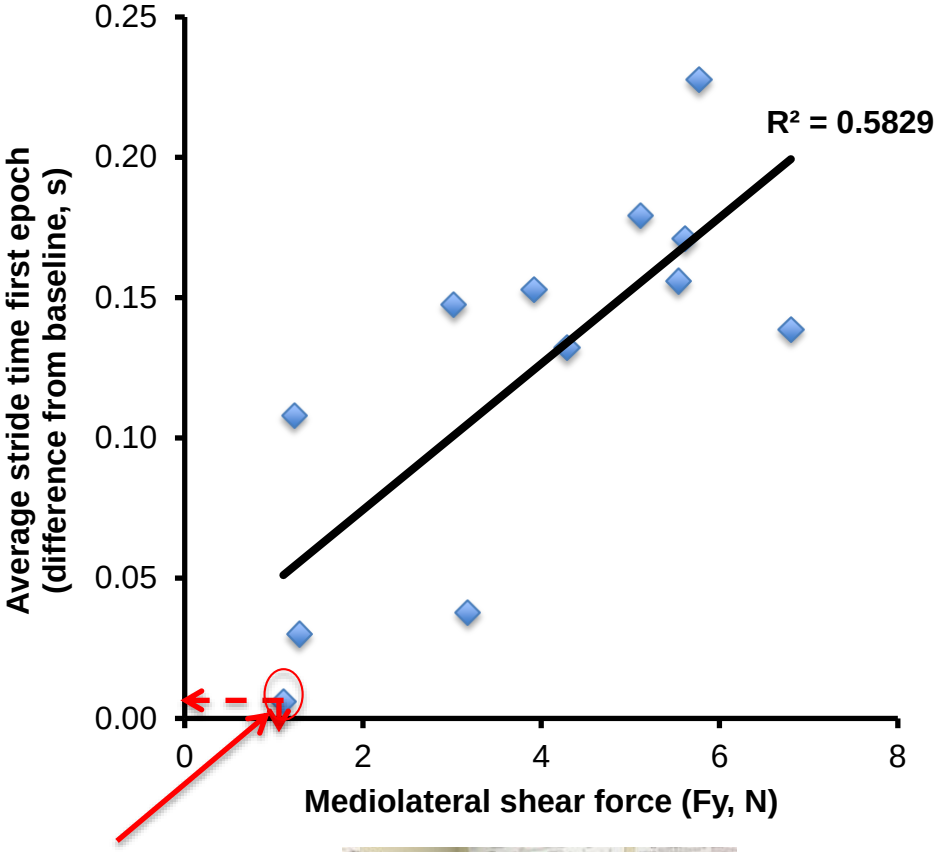
Locomotor Adaptive Challenge

Sensory Bias: *Proprioceptive sensitivity measured by balance control on gravity bed correlates with the ability to respond to a locomotor balance challenge*

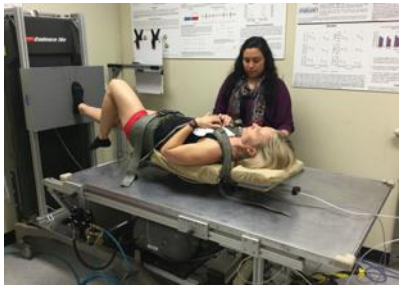




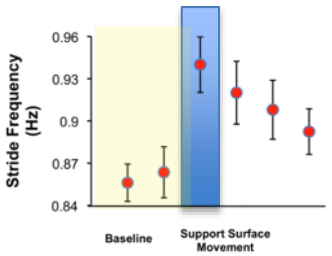
B. Peters, et al. 2014



Best adapter



Motor Learning: *Adaptation rate on the adaptive functional mobility test correlated with the ability to respond to a locomotor balance challenge*



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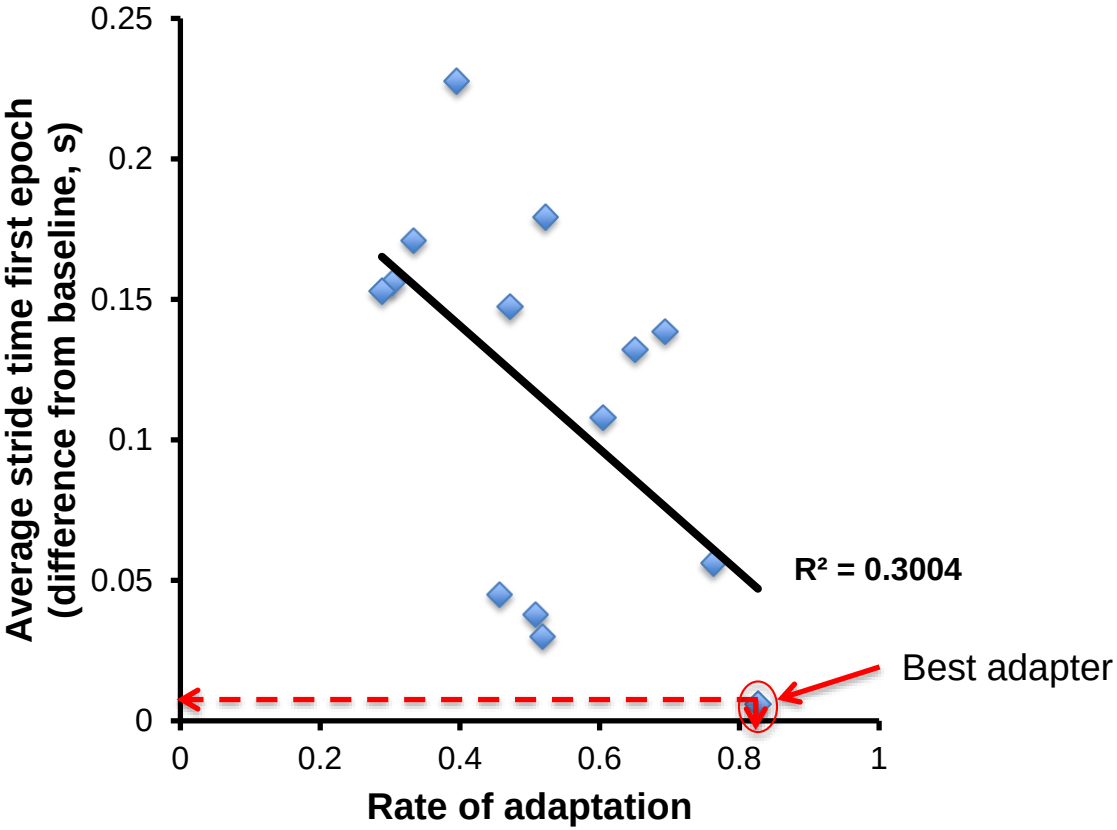
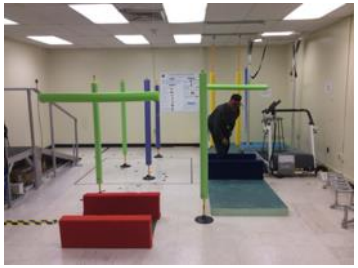
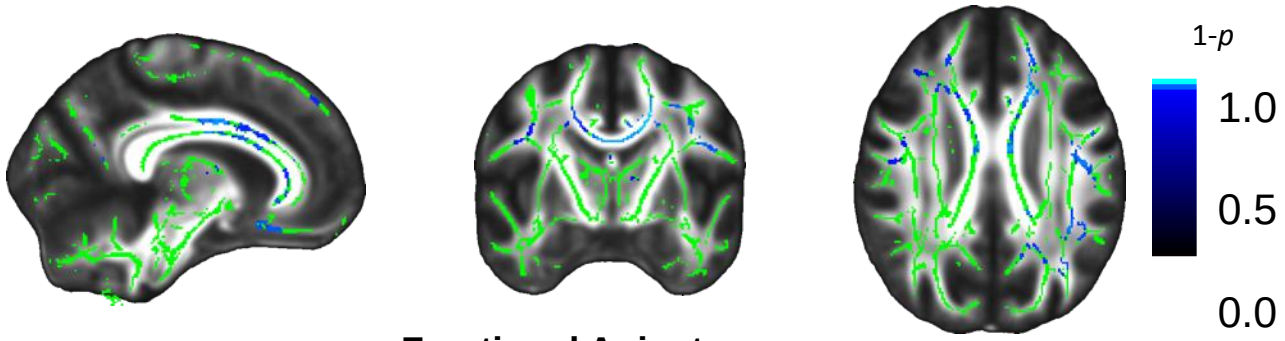
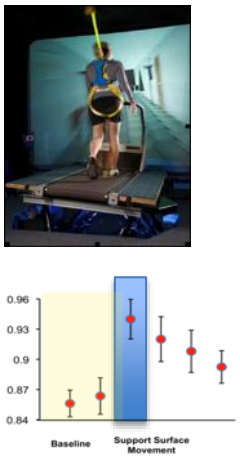


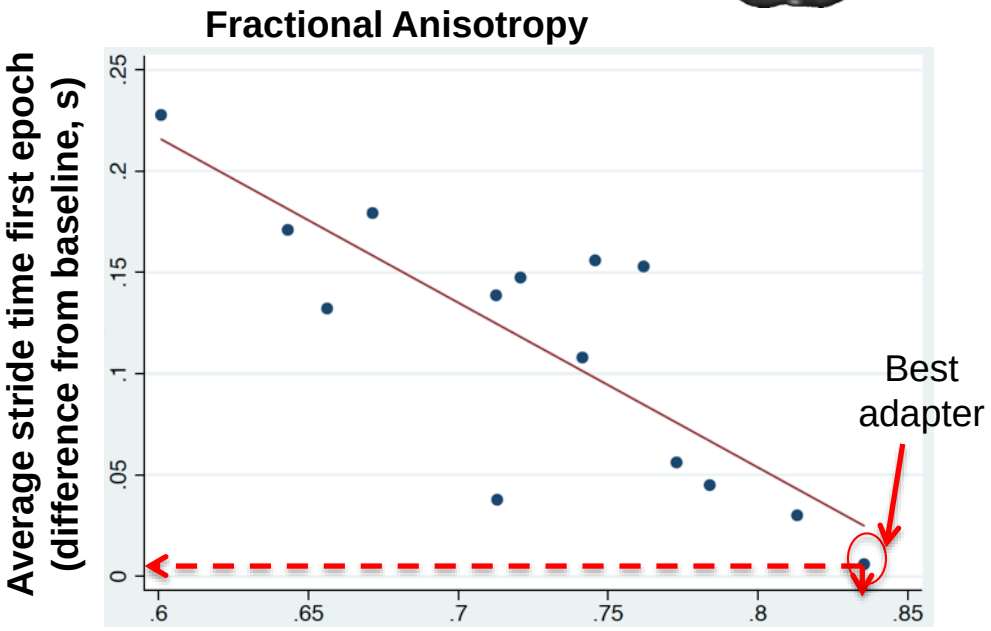


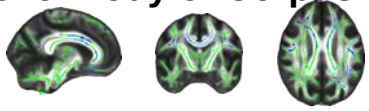
Diffusion Tensor Imaging: *Fractional Anisotropy (FA) of white matter tracts distributed widely over the brain correlated significantly with the ability to respond to a locomotor balance challenge* – e.g. Larger FA measured in the body of corpus callosum corresponds with better adaptability to a locomotor balance challenge.





B. Peters, et al. 2014

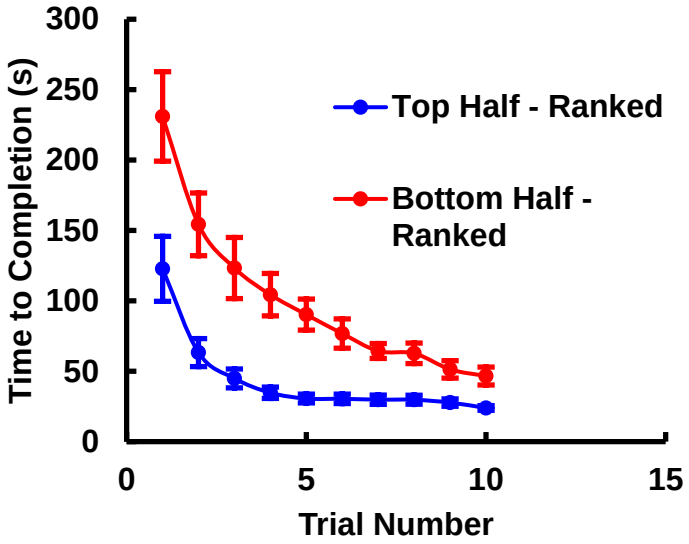




Presence of the alleles - *Met in COMT (rs4680) and Val in BDNF (rs6265) – differentiates visuo-motor adaptation during locomotion*

Adaptive Functional Mobility Test: Negotiate a complex obstacle while wearing up-down vision displacing goggles. Repeated 10 trials. Measure time to complete course (TCC, seconds).17101

	DRD2 rs1076560	COMT rs4680	BDNF rs6265	DraI rs553668
Top Half	7/15 (47%) GG/GT	6/15 (40%) Met-Met/ Met-Val	8/15 (53%) Val-Val	3/15 (20%) 6.7/6.3 kb
	1/15 (7%) TT	2/15 (13%) Val-Val	0/15 (0%) Val-Met	5/15 (33%) 6.7/6.7 kb
Bottom Half	6/15 (40%) GG/GT	3/15 (20%) Met-Met/ Met-Val	2/15 (13.3%) Val-Val	1/15 (6.7%) 6.7/6.3 kb
	1/15 (7%) TT	4/15 (27%) Val-Val	5/15 (33%) Val-Met	6/15 (40%) 6.7/6.7 kb



Results Summary from 16 Normal Subjects

1. Sensory Bias and Motor Learning - Proprioceptive sensitivity along with the rate of visuomotor adaptation on a complex locomotor task correlates with the ability to respond to a locomotor balance challenge.

2. Brain Metrics – FA from DTI, activity during performance of functional task, and connectivity of different regions of brain, have all shown the ability to predict adaptability to locomotor and visuomotor adaptation challenges.

3. Genetic Polymorphisms - COMT (rs4680), BDNF (rs6265) and α_2 - Adrenergic receptor showed presence of specific alleles that differentiated mobility performance during a visuomotor adaptation challenge.

4. These data indicate that individual sensory bias, motor learning ability, brain structural and functional metrics and genetic polymorphisms can be predictive of individual responses to sensorimotor adaptation challenges.

Status of Project

- Science Management Panel (SMP)/Human Research Program (HRP) authority to proceed (May, 2016)
  - Recruit bed rest subjects and management/retired crewmembers
- International Space Station Medical Projects (ISSMP) approved project implementation plan (June, 2016)
- Lifetime Surveillance of Astronaut Health (LSAH) approved sharing archived data for use in this project (July, 2016)
- Recruited total of 6 subjects (4/31 bed rest subject, 2/11 crewmembers)
- Completed data collection of 5 subjects to date; data being analyzed
- SMP/HRP authority to proceed to recruit active flight crewmembers
- Recruitment in progress from an additional list of 18 active crewmembers
- Extend Normative study (N=40)
  - Will determine a set of predictive models using behavioral, brain imaging and genomic measures to determine both change and also the ability to re-adapt sensorimotor and functional performance after long-duration spaceflight post mission.
  - Comparisons of model performance for various groups of predictors will allow implementation of customized sensorimotor adaptability training countermeasures against decrements in functional performance.
- Study End – May 31, 2017.

Thank You

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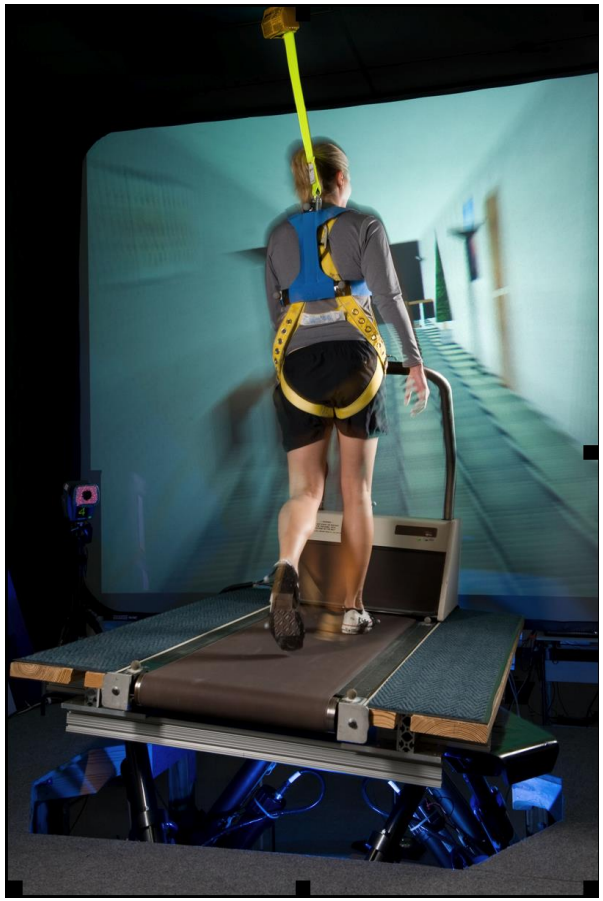
Sensorimotor Adaptability Training

Train on a treadmill with surrogate sensory challenges:

- Altered visual information
- Altered body loading information
- Altered vestibular information (GVS)

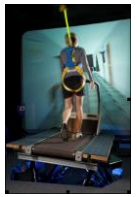


With and without support surface motion (motion base treadmill system)

Sensory Bias Metrics

Tests of Visual Dependency

Treadmill Visual Dependency Test: Subjects will walk on treadmill with incongruent visual flow while measuring torso kinematics.



Rod and Frame Test: Subjects will align a rod to vertical within a tilted frame.

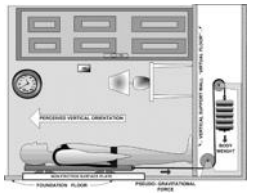
Tests of Vestibular Function

Dynamic Posturography: Subjects will perform tests that parse out vestibular contribution (sway referenced, eyed closed).

Vestibular Threshold: Will assess roll tilt perceptual thresholds in the dark. These tests identify how small of a motion can be distinguished as being left vs. right, which is limited by internal sensory noise levels.

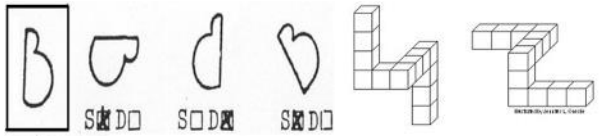
Test of Proprioceptive Dependency

Tests of Proprioception in Balance Performance: Will assess single leg balance control on “gravity bed”.



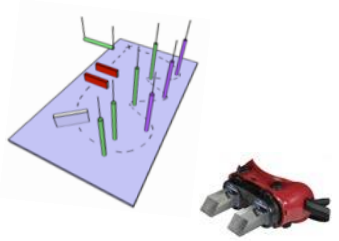
Test of Working Memory

Working memory underlies many daily cognitive operations assessed using two tests: Thurston’s card rotation task ; and Cube rotation task under otolith canal conflict scenario in a Tilt Translation Sled device.



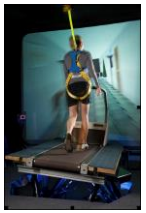
Motor Learning Mode Metrics

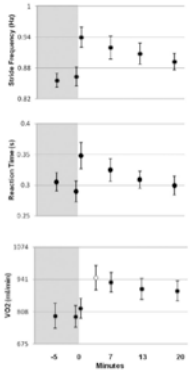
<u>Adaptive Functional Mobility Test</u>: Subjects will negotiate a complex obstacle course placed on medium density foam while wearing up-down vision displacing goggles. This test will be performed 10 times per trial to obtain both strategic learning (during each trial) and plastic-adaptive learning (over repeated trials).



up-down vision displacing goggles

<u>Sensory Discordance Test</u>: This paradigm provides a multisensory assessment of adaptive performance (Peters et al. 2013).

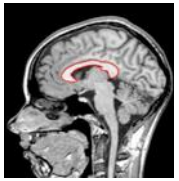


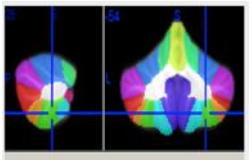


- ***Locomotor Stability***: Stride frequency using foot-switches.
- ***Multi-Tasking Capability*****:** Subject depressed hand-held switch in response to a series of audible tones to measure reaction time.
- ***Metabolic cost***: VO_2 was collected via a portable metabolic gas analysis system.

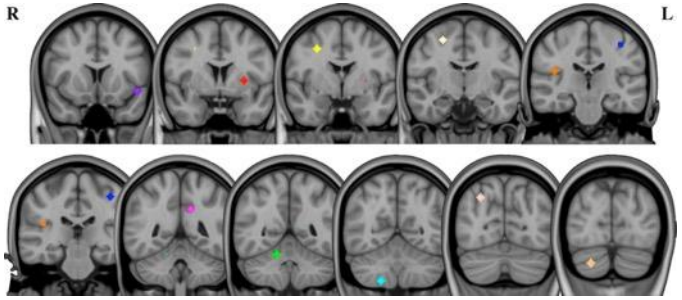
Brain Structural And Functional Metrics

Structural MRI scan: High-resolution anatomical images to assess individual differences in regional brain volumes.

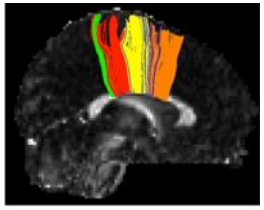




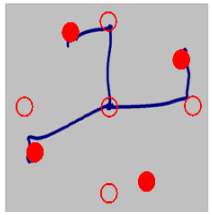
Resting State Functional Connectivity MRI: Strength of communications between “hubs” in the brain’s networks.



Diffusion Tensor Imaging (DTI): Quantify large white matter pathways in the brain and calculate their structural integrity specifically the cortico-spinal tract connecting motor brain regions and the spinal cord, in addition to other pathways.



Functional MRI: fMRI <u>during</u> manual sensorimotor adaptation task identifies brain networks supporting visuomotor plasticity.



Genetic Polymorphisms

Single nucleotide polymorphisms (SNPs) in catechol-O-methyltransferase (COMT, rs4680): COMT *val* homozygotes exhibit slower adaptive changes in a manual sensorimotor adaptation task

SNPs in Dopamine Receptor D2 (DRD2, rs 1076560): Codes for D2 dopamine receptors in the striatum; G>T exhibit slower adaptive changes in a manual sensorimotor adaptation task

SNPs in Brain-derived neurotrophic factor (BDNF, rs6265): BDNF *val/met* carriers exhibit reduced manual sensorimotor adaptation and less retention of adaptive learning

Genetic polymorphism of C10 α_2 - Adrenergic receptor: Associated with individual differences in autonomic responses to stress, including susceptibility to motion sickness

- N = 16 normal subjects
- Saliva samples ORAGENE kit (DNA Genotek, Inc.)
- SeqWright Genomic Services, GE Healthcare, Houston, TX - Custom quantitative PCR (QPCR) assays by designing flanking primers and fluorogenic probes, both specific to target alleles from sequence information or specific pre-optimized TaqMan® assays and signal detection was carried out using an ABI PRISM® Sequence Detection System at an accuracy level of 99.6%.