FOCAL GRAY MATTER PLASTICITY AS A FUNCTION OF LONG DURATION HEAD DOWN TILTED BED REST: PRELIMINARY RESULTS

V. Koppelmans[1], B. Erdeniz[1], Y. E. De Dios[2], S. J. Wood[3, 4], P. A. Reuter-Lorenz[5], I. Kofman[2], J. J. Bloomberg[4], A. P. Mulavara[4,5], and R. D. Seidler[1,5]

[1] School of Kinesiology, University of Michigan, Ann Arbor, MI, USA; [2] Wyle Life Sciences, Houston, TX, USA; [3] Department of Psychology, Azusa Pacific University, Azusa, CA, USA; [4] NASA Johnson Space Center, Houston, TX, USA; [5] Universities Space Research Association, Houston, TX, USA [6] Department of Psychology, University of Michigan, Ann Arbor, MI, USA; [7] Neuroscience Program, University of Michigan, Ann Arbor, MI, USA

BACKGROUND Long duration spaceflight (i.e., 22 days or longer) has been associated with changes in sensorimotor systems, resulting in difficulties that astronauts experience with posture control, locomotion, and manual control. The microgravity environment is an important causal factor for spaceflight induced sensorimotor changes. Whether these sensorimotor changes are solely related to peripheral changes from reduced vestibular stimulation, body unloading, body fluid shifts or that they –may be related to structural and functional brain changes is yet unknown. However, a recent study reported associations between microgravity and flattening of the posterior eye globe and protrusion of the optic nerve [1] possibly as the result of increased intracranial pressure due to microgravity induced bodily fluid shifts [3]. Moreover, elevated intracranial pressure has been related to white matter microstructural damage [2]. Thus, it is possible that spaceflight may affect brain structure and thereby cognitive functioning. Long duration head down tilt bed rest has been suggested as an exclusionary analog to study microgravity effects on the sensorimotor system [4]. Bed rest mimics microgravity in body unloading and bodily fluid shifts. In consideration of the health and performance of crewmembers both in- and post-flight, we are conducting a prospective longitudinal 70-day bed rest study as an analog to investigate the effects of microgravity on brain structure [5]. Here we present results of the first six subjects.

METHODS Six subjects were assessed at 12 and 7 days before-, at 7, 30, and ~70 days in-, and at 8 and 12 days post 70 days of bed rest at the NASA bed rest facility in UTMB, Galveston, TX, USA. At each time point structural MRI scans (i.e., high resolution T1-weighted imaging and Diffusion Tensor Imaging (DTI)) were obtained using a 3T Siemens scanner. Focal changes over time in gray matter density were assessed using the voxel based morphometry 8 (VBM8) toolbox under SPM. Longitudinal processing in VBM8 includes linear registration of each scan to the mean of the subject and subsequently transforming all scans in to MNI space by applying the warp from the mean subject to MNI to the individual gray matter segmentations. Modulation was applied so that all images represented the volume of the original structure in native space. Voxel wise analysis was carried out on the gray matter images after smoothing, using a flexible factorial design with family wise error correction. Focal changes in white matter microstructural integrity were assessed using tract based spatial statistics (TBSS) as part of FMRIB software library (FSL). TBSS registers all DTI scans to standard space. It subsequently creates a study specific white matter skeleton of the major white matter tracts. For each subject, for each DTI metric (i.e. fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)), the maximum value in a line perpendicular to the skeleton tract is projected to the skeleton. Non-parametric permutation based t-tests and ANOVA's were used for voxel-wise comparison of the skeletons.

RESULTS For both VBM and TBSS, comparison of pre bed rest measurements did not show significant differences. VBM analysis revealed decreased gray matter density in bilateral areas including the frontal medial cortex, the insular cortex and the caudate (see Figure) from 'pre to in bed rest'. Over the same time period, there was an increase in gray matter density in the cerebellum, occipital-, and parietal cortex, including the precuneus (see Figure). The majority of these changes did not recover from 'during to post bed rest'. TBSS analysis did not reveal significant changes in white matter microstructural integrity after correction for multiple comparisons. Uncorrected analyses ($p<.015$) revealed an increase in RD in the cerebellum and brainstem from pre bed rest to the first week in bed rest that did not recover post bed rest.

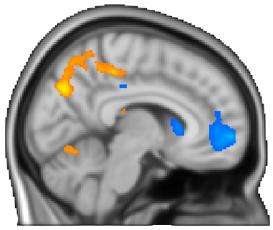

Figure. VBM results projected on the MNI standard brain. Red to yellow color codings indicate increased gray matter density from 'pre to in bed rest'. Blue to light blue color codings indicate decreased gray matter density from 'pre to in bed rest'. Brighter colors indicate larger significance.

DISCUSSION Extended bed rest, which is an analog for microgravity, can result in gray matter changes and potentially in microstructural white matter changes in areas that are important for neuro motor behavior and cognition. These changes did not recover at two weeks post bed rest. Whether the effects of bed rest wear off at longer times post bed rest, and if they are associated with behavior are important questions that warrant further research.

REFERENCES [1] Kramer, L.A., et al. (2012) *Radiology* 263(3), 819-27. [2]Hattori, T., et al. (2012) *Am J Neuroradiol* 33(1), 97-103. [3] Hoffmann, J., et al. (2013) *Cephalalgia* 33(13), 1075-84. [4] Reschke MF et al. (2009) *Aviat Space Environ* 9; 80(5, Suppl.):A1–10. [5] Koppelmans, V., et al. (2013) *BMC Neurology* Submitted for publication.