

## EXERCISE EFFECTS ON THE BRAIN AND SENSORIMOTOR FUNCTION IN BED REST

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Long duration spaceflight microgravity results in cephalad fluid shifts and deficits in posture control and locomotion. Effects of microgravity on sensorimotor function have been investigated on Earth using head down tilt bed rest (HDBR). HDBR serves as a spaceflight analogue because it mimics microgravity in body unloading and bodily fluid shifts. Preliminary results from our prior 70 days HDBR studies showed that HDBR is associated with focal gray matter (GM) changes and gait and balance deficits, as well as changes in brain functional connectivity. In consideration of the health and performance of crewmembers we investigated whether exercise reduces the effects of HDBR on GM, functional connectivity, and motor performance. Numerous studies have shown beneficial effects of exercise on brain health. We therefore hypothesized that an exercise intervention during HDBR could potentially mitigate the effects of HDBR on the central nervous system.

Eighteen subjects were assessed before (12 and 7 days), during (7, 30, and ~70 days) and after (8 and 12 days) 70 days of 6-degrees HDBR at the NASA HDBR facility in UTMB, Galveston, TX, US. Each subject was randomly assigned to a control group or one of two exercise groups. Exercise consisted of daily supine exercise which started 20 days before the start of HDBR. The exercise subjects participated either in regular aerobic and resistance exercise (e.g. squat, heel raise, leg press, cycling and treadmill running), or aerobic and resistance exercise using a flywheel apparatus (rowing). Aerobic and resistance exercise intensity in both groups was similar, which is why we collapsed the two exercise groups for the current experiment.

During each time point T1-weighted MRI scans and resting state functional connectivity scans were obtained using a 3T Siemens scanner. Focal changes over time in GM density were assessed using voxel based morphometry (VBM8) under SPM. Changes in resting state functional connectivity was assessed using both a region of interest (ROI, or seed-to-voxel) approach as well as a whole brain intrinsic connectivity (i.e., voxel-to-voxel) analysis. For the ROI analysis we selected 11 ROIs of brain regions that are involved in sensorimotor function (i.e., L. Insular C., L. Putamen, R. Premotor C., L.+R. Primary Motor C., R. Vestibular C., L. Posterior Cingulate G., R. Cerebellum Lobule V + VIIIb + Crus I, and the R. Superior Parietal G.) and correlated their time course of brain activation during rest with all other voxels in the brain. The whole brain connectivity analysis tests changes in the strength of the global connectivity pattern between each voxel and the rest of the brain. Functional mobility was assessed using an obstacle course. Vestibular contribution to balance was measured using Neurocom Sensory Organization Test 5. Behavioral measures were assessed pre-HDBR, and 0, 8 and 12 days post-HDBR. Linear mixed models were used to test for effects of time, group, and group-by-time interactions.

Family-wise error corrected VBM revealed significantly larger increases in GM volume in the right primary motor cortex in bed rest control subjects than in bed rest exercise subjects. No other significant group by time interactions in gray matter changes with bed rest were observed. Functional connectivity MRI revealed that the increase in connectivity during bed rest of the left putamen with the bilateral midsagittal precunes and the right cingulate gyrus was larger in bed rest control subjects than in bed rest exercise subjects. Furthermore, the increase in functional connectivity with bed rest of the right premotor cortex with the right inferior frontal gyrus and the right primary motor cortex with the bilateral premotor cortex was smaller in bed rest control subjects than in bed rest exercise subjects. Functional mobility performance was less affected by HDBR in exercise subjects than in control subjects and post HDBR exercise subjects recovered faster than control subjects. The group performance differences and GM changes were not related.

Exercise in HDBR partially mitigates the adverse effect of HDBR on functional mobility, particularly during the post-bed rest recovery phase. In addition, exercise appears to result in differential brain structural and functional changes in motor regions such as the primary motor cortex, the premotor cortex and the putamen. Whether these central nervous system changes are related to motor behavioral changes including gait and balance warrants further research.