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| **Fiscal Year:** | FY 2021 | **Task Last Updated:** | FY 02/14/2022 |
| **PI Name:** | Stahn, Alexander Ph.D. | | |
| **Project Title:** | Hyper.Campus - Effects of Artificial Gravity on Structural and Functional Plasticity During Head-Down Tilt Bed Rest | | |
| **Division Name:** | Human Research | | |
| **Program/Discipline:** | | | |
| **Program/Discipline--Element/Subdiscipline:** | | | |
| **Joint Agency Name:** | | **TechPort:** | No |
| **Human Research Program Elements:** | (1) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H) | | |
| **Human Research Program Risks:** | (1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders | | |
| **Space Biology Element:** | None | | |
| **Space Biology Cross-Element Discipline:** | None | | |
| **Space Biology Special Category:** | None | | |
| **PI Email:** | astahn@pennmedicine.upenn.edu | **Fax:** | FY |
| **PI Organization Type:** | UNIVERSITY | **Phone:** | 215-898-9667 |
| **Organization Name:** | University of Pennsylvania | | |
| **PI Address 1:** | Division of Sleep and Chronobiology, Department of Psychiatry | | |
| **PI Address 2:** | 423 Guardian Dr, 1016 Blockley Hall | | |
| **PI Web Page:** | | | |
| **City:** | Philadelphia | **State:** | PA |
| **Zip Code:** | 19104-4865 | **Congressional District:** | 3 |
| **Comments:** | | | |
| **Project Type:** | Ground | **Solicitation / Funding Source:** | 2015-16 HERO NNJ15ZSA001N-AGBR. Appendix G: Physiological & Behavioral Responses in Humans to Intermittent Artificial Gravity during Bed Rest |
| **Start Date:** | 04/10/2018 | **End Date:** | 08/31/2021 |
| **No. of Post Docs:** | | **No. of PhD Degrees:** | |
| **No. of PhD Candidates:** | | **No. of Master' Degrees:** | 1 |
| **No. of Master's Candidates:** | 1 | **No. of Bachelor's Degrees:** | |
| **No. of Bachelor's Candidates:** | | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Whitmire, Alexandra | **Contact Phone:** | |
| **Contact Email:** | alexandra.m.whitmire@nasa.gov | | |
| **Flight Program:** | | | |
| **Flight Assignment:** | NOTE: End date changed to 8/31/2021 per NSSC information (Ed., 1/11/21) | | |
| **Key Personnel Changes/Previous PI:** | February 2022 final report: CoInvestigators changed in the past two years; see CoInvestigator field for FY2021 vs. FY2020 report. February 2019 report: Two PhD students, who are critical to the study, are included as key to study implementation: • Anika Werner, Charite - Universitatsmedizin Berlin, Institute of Physiology, Center for Space Medicine and Extreme Environments Berlin, CharitéCrossOver (CCO), Charitéplatz 1, Virchowweg 6, 10117 Berlin, Email: anika.werner@charite.de, and Katharina Brauns, Charite - Universitatsmedizin Berlin, Institute of Physiology, Center for Space Medicine and Extreme Environments Berlin, CharitéCrossOver (CCO), Charitéplatz 1, Virchowweg 6, 10117 Berlin, Email: Katharina.brauns@charite.de | | |

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| **COI Name (Institution):** | Dinges, David Ph.D. ( University of Pennsylvania )<br>Gunga, Hanns-Christian M.D. ( Charite - Universitatsmedizin Berlin, Germany )<br>Gur, Ruben Ph.D. ( University of Pennsylvania )<br>Kuehn, Simone Ph.D. ( Max Planck Institute for Human Development Berlin, Germany )<br>Roalf, David Ph.D. ( University of Pennsylvania )<br>Basner, Mathias M.D., Ph.D. ( University of Pennsylvania )<br>Garcia, Caroline Ph.D. ( University Medical Center Hamburg-Eppendorf )<br>Hartley, Tom Ph.D. ( University of York )<br>Riecke, Bernhard Ph.D. ( Simon Fraser University )<br>Miller, Noah Ph.D. ( Simon Fraser University )<br>Moore, Tyler Ph.D. ( University of Pennsylvania )<br>Friedl-Werner, Anika Ph.D. ( Charité-Universitätsmedizin Berlin )<br>Brauns, Katharina Ph.D. ( Charité-Universitätsmedizin Berlin ) |
| **Grant/Contract No.:** | 80NSSC18K0765 |
| **Performance Goal No.:** | |
| **Performance Goal Text:** | |
| **Task Description:** | This project addressed the risk of Adverse Behavioral Conditions and Psychiatric Disorders, and the need to validate countermeasures that promote individual behavioral health and performance during exploration class missions. As part of the NASA/ESA AGBRESA (NASA/European Space Agency/Artificial Gravity Bed Rest – European Space Agency) study we investigated the effects of artificial gravity (AG) as a countermeasure during 60 days of head down tilt bed rest (HDBR) on brain changes and its behavioral significance. N=24 subjects were randomly allocated to one of three groups: (1) HDBR only (N=8); (2) HDBR plus daily intermittent AG comprising of 6 bouts of 5 min AG (N=8); and (3) HDBR plus daily continuous AG comprising of 30 min AG (N=8). We identified structural and functional brain changes using magnetic resonance imaging (MRI), and specifically targeted neural correlates of spatial cognition, i.e., the hippocampal formation, parahippocampus, insula, striatum, caudate nucleus, and precuneus. Spatial abilities were investigated using a variety of tasks assessing spatial updating, path integration, perspective taking, wayfinding, and spatial learning and memory formation. Given that spatial abilities are also tightly coupled to executive functions, we additionally administered two paradigms to quantify flexible coordination of multiple task-sets using a switching task, and a dual task based on a psychological refractory period paradigm. Furthermore, we used the Cognition test battery to screen changes in general cognitive performance. Finally, we also collected blood and saliva samples to identify the time course of key neurotrophins (i.e., BDNF, IGF-1, VEGF, NF-L) and pro-inflammatory markers (i.e., Il-1b, Il-6, and TNFa) associated with the effects of bed rest and AG. To assess the acute effects of the AG countermeasure, blood samples were collected in the morning as well as after selected AG sessions. Together, these data provide important information about the neurophysiological mechanisms and pathways related to the effects of HDBR and the AG countermeasure. The study had the following specific aims (SA):<br>SA 1: Investigate the effects of HDBR with and without artificial gravity on gray and white matter volume, subcortical volume, myelination, functional connectivity, and task-related brain activation: We assessed subjects with quantitative structural and functional MRI before, during, and after HDBR.<br><br>SA 2: Investigate the effects of HDBR with and without artificial gravity on cognitive performance: To assess the relation between brain structural and functional changes and changes in cognitive performance, we performed a unique set of sensitive but unobtrusive cognitive measurement tools with and without MRI before, during, and after HDBR. The tasks are designed and scheduled to avoid any masking effects due to repetitive testing and/or changing body posture, and specifically probe the anatomical correlates that were expected to be most vulnerable to the detrimental effects of HDBR, i.e., the hippocampus, the cingulate cortex, and the prefrontal cortex.<br><br>SA 3: Investigate the effects of HDBR with and without artificial gravity on biochemical markers of stress and neuroplasticity: We took sample blood and saliva samples after an overnight fast in the morning two times bed rest, five times during bed rest, and two times after bed rest. In addition, five blood samples were taken during bed rest immediately after the AG intervention. These samples will be analyzed for BDNF, IGF- 1, VEGF, NF-L, Il-1b, Il-6, and TNFa. At identical time points we also collected a saliva sample in the morning and evening to assess changes in cortisol levels. These data were expected to provide valuable information for the potential underlying neurophysiological mechanisms and pathways related to the effects of HDBR and the AG countermeasure. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | With the proposed work we relevantly contributed to the goal of the Human Research Program (HRP) to provide human health and performance countermeasures, knowledge, technologies, and tools to enable safe, reliable, and productive human space exploration. Combing neuroimaging, biochemical and behavioral data our results support the development of countermeasures and provide mission planners and system developers with strategies for monitoring and mitigating crew health and performance risks during long-duration space missions. Moreover, exploring the neurobehavioral effects of bed rest and their mechanisms promotes research on the role of inactivity in health and disease on Earth. This could have implications for situations or conditions in which physical activity levels become severely restricted, including medical conditions like myotonic dystrophy and fibromyalgia, prolonged physical inactivity due to confinement to bed rest in clinical settings, and a lack of inactivity associated with sedentary lifestyles. |
| | The study was performed at German Space Agency (DLR) DLR :envihab ( <a target="_blank" href="https://www.dlr.de/envihab/en/desktopdefault.aspx/tabid-6890/">https://</a> ), and involved two campaigns of 12 participants each. Data for the first campaign were collected between February and June 2019. Eight men and four women participated in this campaign and had the following group assignments: bed rest only (CTRL) (3 men, 1 woman), bed rest with continuous artificial gravity exposure (cAG) (3 men, 1 woman), and bed rest with intermittent artificial gravity exposure iAG (2 men, 2 women). In August 2019 twelve participants (6 men, 6 women) were recruited for the second campaign. Due to an unprecedented number of personal withdrawals and medical drop-outs, five subjects had to be replaced. The final sample included the target N=24 subjects with N=8 CTRL (6 men, 2 women, mean age: 35 yrs), N=8 cAG (5 men, 3 women, mean age: 32 yrs), and N=8 iAG (5 men, 3 women, mean age: 34 yrs). Data collection |

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| **Task Progress:** | was completed in December 2019. Overall, data acquisition rates and data quality were excellent. We collected 7438 data points out of a total of 7592 (97.9%). The main findings for specific aim are summarized below.<br>Aim 1: Investigate the effects of HDBR with and without artificial gravity on Brain Structure and Function. We hypothesized that long-duration bed rest would impair brain structure and function, and that these effects would most affect brain areas associated with spatial cognition. Our findings confirmed this hypothesis as indicated by significant decreases in bilateral gray matter volume of the insula and reductions of the right dentate gyrus volume in response to bed rest. We also expected that any adverse neurobehavioral effects would be reduced by the AG countermeasure. This was confirmed by stability of insula and dentate gyrus volumes in both intervention groups receiving the AG countermeasure. Mean reductions in dentate gyrus volume during bed rest were significantly associated with increased mean concentrations of NF-L, a marker of axonal injury and degeneration. We also identified several significant correlations between changes in insula gray matter volumes and changes in NF-L, IGF-1, TNFa, and Il-1b. The changes in dentate gyrus volume were significantly associated with changes in cognitive performance. We observed a significant relationship between changes in accuracy of the Four Mountains Task, a task included in the Spatial Cognition battery and assessing allocentric spatial memory formation. In addition, we found a nearly significant correlation between changes in dentate gyrus volume and performance of the Emotion Recognition Task of the Cognition battery. In line with that, task functional imaging using the emotion recognition task showed a reduced BOLD response after 59 days of bed rest.<br><br>Aim 2: Investigate the effects of HDBR with and without artificial gravity on cognitive performance. The emotion recognition task of the Cognition battery revealed a gradual decrease in speed during HDBR. With increasing time spent in HDBR, participants required longer time to decide which facial emotion was expressed. The Cognition survey also showed that participants were also more likely to select categories with negative valence over categories with neutral or positive valence. Except for workload, which was rated lower in the CTRL group, continuous or intermittent AG did not modify the effect of HDBR on cognitive performance or subjective responses. These findings are very much in line with data that we collected using two standard tasks to assess executive control, i.e., a switching and dual task paradigm performed before and after HDBR, which did not reveal any clear interactions of performance between experimental groups in response to HDBR. Spatial Cognition batteries suggested a tendency for improved performance in the AG countermeasure groups relative to CTRL. Precision numerically decreased for the most difficult condition in the Spatial Updating Task in CTRL during HDBR relative baseline, whereas performance in iAG and cAG remained stable. We also found higher improvements in precision in medium (2-Turn) and difficult (3-Turn) conditions of the Point to Origin Task in iAG compared to cAG and CTRL. Likewise, response speed in the Four Mountains Task, which is a task assessing topographical mapping, was significantly increased during HDBR relative to baseline in iAG and cAG, but not CTRL. Accuracy in the Four Mountains Task also significantly increased during HDBR in iAG, but not in cAG and CTRL. The Cognitive Mapping Task revealed a considerable (though not statistically significant) effect for cAg and iAG, suggesting the AG supported the ability to accurately integrate new spatial memories into a cognitive map, a process which is hypothesized to significantly rely on hippocampal activation. Along these lines we observed numerically higher accuracy scores in cAG and iAG relative to CTRL in the Plus Maze for conditions that required subjects to switch from an egocentric response to an allocentric navigational strategy. Finally, we observed similar effects (again, not statistically significant though) for efficiency of a classical paradigm to assess spatial orientation, the Spatial Orientation Task. In summary, these data suggest potential benefits of the AG countermeasure, and particularly iAG on spatial cognition. This was also reflected when accuracy, speed, and efficiency were summarized across tasks, which showed the changes in accuracy from baseline to HDBR are significantly larger in iAG compared to the changes from baseline in cAG and CTRL. However, given the small sample sizes and variation between groups, these effects need to be interpreted cautiously, and require confirmation in further studies.<br><br>Aim 3: Investigate the effects of HDBR with and without artificial gravity on biochemical markers of stress and neuroplasticity. Analyses of the acute molecular responses to AG showed a significant increase in IGF-1, and a significant decrease in NF-L and TNFa after the AG intervention compared to before AG. This was effect was observed in both iAG and cAG. Furthermore, cAG was characterized by an increase in Il-1b following the AG exposure. Given that the daily timing of the AG intervention varied between and within subjects, it remains unclear whether the results can be attributed to the intervention, or, are at least somewhat caused by biological rhythms. The sample before AG was always collected in the morning after an overnight fast, whereas the sample after AG was collected immediately after completion of the AG exposure. Because no data were collected at identical time points in the CTRL group, we cannot verify whether the observed acute molecular changes were affected by circadian variation. IGF-1 also showed the most pronounced effect in response to HDBR. IGF-1 was upregulated in response during HDBR, and then decreased again during the recovery irrespective of the experimental group. Il-6 and TNFa considerably peaked on the first day of recovery, whereas the effect for Il-6 was slightly, but significantly, more pronounced in CTRL compared to iAG and cAG. Given the potent role of IGF-1 in modulating neuronal transmission, metabolism and morphology, and neuroprotective capacities, on the one hand, and the role of NF-L and TNFa as predictors for cognitive decline, and neuropathological conditions on the other, future studies are needed to clarify the potential of AG to positively affect the molecular dynamics associated with neurobehavioral adaptations. |
| **Bibliography Type:** | Description: (Last Updated: 11/07/2024) |
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