Protocol for the Study

Temporal Nature of Cognitive and Visuospatial Brain Domain Changes During Long-Duration Low-Earth Orbit Missions (Spatial Cognition)

NASA Grant 80NSSC19K1046
NASA Johnson Space Center IRB Protocol STUDY00000175

Date: 7/31/2020

1.1 Study Identification Information

a) Study Name:

Temporal Nature of Cognitive and Visuospatial Brain Domain Changes During Long-Duration Low-Earth Orbit Missions (Spatial Cognition)

b) Brief Synopsis / Abstract:

This is an international proposal consisting of two projects with synergistic aims that will be carried out in a joint effort by NASA and DLR/ESA. It addresses the HRP Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders, HRP's requirement to demonstrate the presence or absence of unacceptable deleterious neurocognitive effects beyond the experience base of six-month expeditions, and to permit extrapolation to early interplanetary expeditions. It also addresses several other critical HRP risks and gaps (e.g., BMed1, BMed2, BMed3, BMed5, CNS-1, SM26). More specifically, we will target NASA's particular interest in studying the 'Cognitive-perceptual-visuospatial brain domain changes due to isolation and confinement' as part of the integrated One-Year Mission Project (i1YMP) on the International Space Station (ISS). The data we propose to collect will - for the first time - reliably demonstrate whether prolonging mission duration to one year will have detrimental effects on general cognitive performance (measured with the Cognition test battery), spatial cognition, structural and functional brain changes in general, and hippocampal plasticity more specifically relative to the shorter 6-month and 2-month missions. Using state-of-the-art neuroimaging techniques, we will determine the biological basis for any changes in cognitive performance, with a focus on hippocampal plasticity. Similar data already gathered on the ISS and in several short- and long-duration space analog environments will be used to generate a normative data base for long-duration missions. Finally, we will derive dose-response relationships between cognitive-visuospatial brain domain changes and mission duration that will allow predicting vulnerability to adverse cognitive or behavioral impairment and psychiatric disorders on interplanetary expeditions such as a mission to Mars. The two 7-yr projects will deliver a highly unique and comprehensive set of integrated neuroimaging and neurocognitive tools for the evaluation and ultimately prevention of adverse effects on brain structure and function that lead to behavioral effects associated with exploration-type missions.

c) Is this a Ground-Based or Space Flight study?

__X__Ground-Based Study: Control subjects
__X__Space Flight Study: ISS

d) What type of data does the research study require?

_____Prospective: Collecting new data
_____Retrospective: Use of archived data
__X__Both: Combination of new and archived data

If "**Retrospective**" is selected above, PI must submit a data request through the NASA's LSDA/LSAH Data Request Portal at the following link (https://lsda.jsc.nasa.gov/) to obtain the LSAH-AB feasibility letter that MUST accompany your eIRB protocol submittal.

If **"Both"** is selected above, please ensure both the prospective and retrospective components are clearly covered in the Informed Consent Form.

Investigators requesting NASA subject(s) archived data, agree that ALL publications resulting from this project will be submitted to LSAH for privacy review before submission for publication, including presentations, abstracts, and manuscripts.

e) Name of Co-Principal Investigators
Mathias Basner, MD, PhD, MSc
Alexander C. Stahn, PhD

1.2 External Review and Approval

Has the protocol been reviewed by another institution? ____Yes __X__ No

If "yes", what was the disposition or determination of the external review? Please list the institution, board and contact information where this protocol was or will be reviewed.

1.3 Conflict of Interest

Do any of the participating study investigators or other research personnel (or their immediate family/significant other) have a financial and/or intellectual property interest in the sponsor or products used with this project?
____Yes __X__No

If "yes", Conflicts of interest statements must be submitted by all key personnel on dated, signed, institutional letterhead with the study title identified. The letter must answer affirmatively and disclose the relationship with the company or entity arrangements. A related financial interest does NOT automatically mean that the investigator cannot participate in the research. The IRB will determine if the financial and or other conflict of interest can be reduced, eliminated or managed in order to allow participation in the research project.

If “no”, Conflicts of interest statements must be submitted by all key personnel on dated, signed, institutional letterhead with the study title identified. The letter must include the following statement:

> “I do not receive any research support from non-public sponsors of research. I do not perform any validation research of a drug or device. I do not receive any gifts or income from individuals associated with my research studies. I do not use my position with_____(fill in the blank with name of employer, i.e. NASA, KBRWyle etc) or proprietary or confidential information obtained in performing my duties, in any marketing, investing, or commercial ventures.

1.4 Study Funding Information

Has funding been awarded for this study? Yes __X__ No ____

If “yes”, please list all sources of funding:
NASA grant 80NSSC19K1046 (Definition Phase)
DLR grant (number not yet assigned)

Please list the funded study title if different from the Study Name listed in this protocol submission:
N/A

1.5 Scientific Merit Assessment

Has this study received a scientific merit assessment? Yes__X__ No ____

If “yes”, what organization, review body and or individual conducted the review?
NASA

If “no”, has there been a technical assessment?

Has this study been modified since the last merit review?
Yes
If so please describe all modifications to the study:
The project is funded for a definition phase first. Any changes identified during the definition phase will be addressed in an amendment to this protocol.

1.6 Human Genetic Testing

Does the NASA Policy Directive 7170, Use of Human Research Genetic Testing, apply to this study? Yes____ No__X__

If “yes”, please mark the study as greater than minimal risk in the protocol document (Section 2.1.a)) and answer the following questions.

Human Genetic Testing Procedures

a) What is the purpose of the human research genetic testing?

b) Will the human research genetic data be extracted from biospecimens?
Yes___ No_____

c) Please describe the process for human research genetic data extraction from the subject and then from the subsequent sample.

d) Please provide a plan to protect human research genetic test data. The following are required to be included or addressed in the plan:

i) Please state that attributable or identifiable human research genetic data will not be publicly released without the prior approval of the individual research subject and other subjects whose anonymity might be affected by the release, as well as the NASA IRB or the Lifetime Surveillance of Astronaut Health Advisory Board.
ii) Outline the procedures to protect the privacy of genetic information. (Including after death of the subject, to avoid unwarranted invasion of personal privacy of surviving family members.)
iii) Please state that no whole genomic sequence data will be published or made public without written consent from the subject or their direct family members who may be impacted by the release of the data.
iv) Please state that all human research genetic testing data will be considered protected data for the purposes of safeguards.
v) Please state that results from human research genetic testing will not be data-mined or cross-referenced with other databases of any kind unless approved by the NASA IRB.
vi) Please state that investigators will not attempt to identify or contact individual participants from whom data was collected without approval from the NASA IRB.
vii) Because it may be possible to reidentify deidentified genomic data, please describe how this research data will be controlled.
viii) Any human research genetic data will be stored in a database separately from data containing personally identifiable information (e.g., sex, age, name, address, phone number, social security number), unless it has been included in the research subject’s Electronic Medical Record (EMR).
N/A

e) **Please describe the plan to provide genetic counseling. In the plan, please name the genetic counselor(s).**

f) **Please provide the plan to adhere to IT security and privacy policy practices.**

g) **Please describe the reporting plan for any inadvertent data release, breach of data security, or other data management incidents.**

h) **Please provide a plan describing the process to archive at NASA (or elsewhere), return original study data, and destroy all copies of the original study data after the study is complete.**

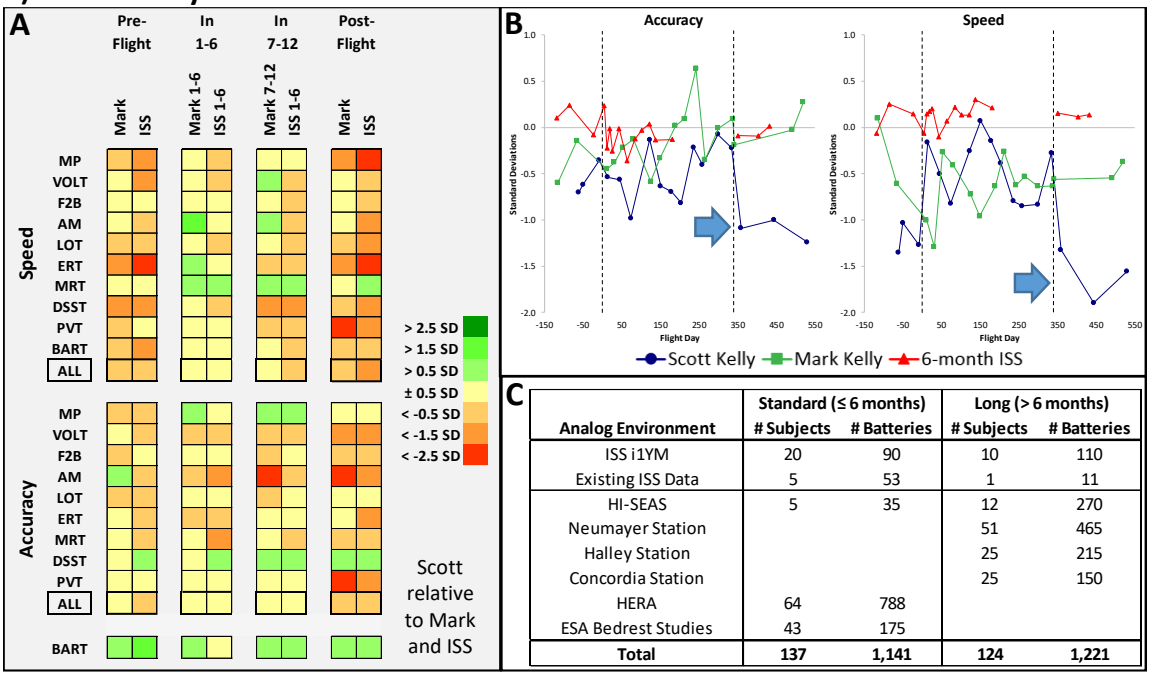
2.0 Background and Significance

a) **Background and Significance:** Successful human space exploration depends on the integrity of a range of cognitive abilities. In addition to the physiological effects of microgravity, spaceflight involves exposure to multiple environmental (e.g., radiation) and psychological stressors related to living in an isolated, confined, and extreme (ICE) environment that have the potential to degrade astronaut cognitive performance and jeopardize mission success. On the first human mission to Mars, astronauts will spend unprecedented times in space beyond low earth orbit. Our knowledge on how humans will cope with living for prolonged periods of time in an ICE environment is extremely limited (only 4 humans have spent consecutively more than 1 year in space). Studies investigating the neurocognitive effects of living in ICE environments beyond the standard 6-month ISS mission are therefore critically needed to (1) understand the effects on brain plasticity and cognitive performance, (2) demonstrate and verify the techniques needed to monitor, diagnose, and prevent such effects, (3) establish a baseline for proposed Deep Space Gateway expeditions of up to 7 months and up to 400 days in the Deep Space Transport, and (4) allow for the confident prediction of adverse neurocognitive trends out to two to three years of typical Mars conjunction-class missions.

This proposal addresses the HRP Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders and HRP's requirement to demonstrate the presence or absence of unacceptable deleterious neurocognitive effects beyond the experience base of six-month expeditions and to permit extrapolation to early interplanetary expeditions. It also addresses several other critical HRP risks and gaps (e.g., BMed1, BMed2, BMed3, BMed5, CNS-1, SM26). More specifically, we will target NASA's particular interest in studying the 'cognitive-perceptual-visuospatial brain domain changes due to isolation and confinement' and in 'operationally-relevant behavioral health and performance

tools' as part of the integrated One-Year Mission Project (i1YMP) on the International Space Station (ISS). The data we propose to collect will - for the first time - reliably demonstrate whether prolonging mission duration to one year will have detrimental effects on general cognitive performance, spatial cognition and hippocampal plasticity relative to the shorter 6-month and 2-month missions. Using state-of-the-art neuroimaging techniques, we will determine the biological basis for any changes in cognitive performance, with a focus on hippocampal plasticity. Similar data already gathered on the ISS, in several space analog environments, and in astronaut and astronaut-surrogate control groups will be used to generate a normative data base for long-duration missions. Finally, we will derive dose-response relationships between cognitive-visuospatial brain domain changes and mission duration that will allow predicting vulnerability to adverse cognitive or behavioral impairment and psychiatric disorders on interplanetary expeditions such as a mission to Mars. The two 7-yr projects will deliver a highly unique and comprehensive set of integrated neuroimaging and neurocognitive tools for the evaluation and ultimately prevention of adverse effects on brain structure and function that lead to behavioral effects associated with exploration-type missions. To meet these objectives, we propose an international collaboration combining two projects that will address synergistic objectives and specific aims.

b) Preliminary Studies:



C

Analog Environment	Standard (≤ 6 months) # Subjects	Standard (≤ 6 months) # Batteries	Long (> 6 months) # Subjects	Long (> 6 months) # Batteries
ISS i1YM	20	90	10	110
Existing ISS Data	5	53	1	11
HI-SEAS	5	35	12	270
Neumayer Station			51	465
Halley Station			25	215
Concordia Station			25	150
HERA	64	788		
ESA Bedrest Studies	43	175		
Total	**137**	**1,141**	**124**	**1,221**

Figure 1: Panel A: This panel shows standardized differences of Cognition performance of Scott Kelly (SK) pre-flight, early in-flight (months 1-6), late in-flight (months 7-12), and post-flight relative to his twin brother Mark (MK) and to 5 astronauts on standard 6-month ISS missions (ISS) (published in the journal *Science* in April 2019). SK showed a slight decline in cognitive speed and accuracy across a range of cognitive domains late in-flight compared to the 6-monthh ISS crew, and a more pronounced decline in performance post-flight compared to both his brother and the 6-monthh ISS crew. This suggests minor effects of prolonging mission duration from 6 to 12 months, but more major effects for the post-flight period. This study will increase our knowledge base from N=1 to N=11. (MP: Motor Praxis; VOLT: Visual Ob-ject Learning; F2B: Fractal 2-Back; AM: Abstract Matching; LOT: Line Orientation; ERT: Emotion Recognition; MRT: Matrix Reasoning; DSST: Digit Symbol Substitution; PVT: Psychomotor Vigilance; BART: Balloon Analog Risk; ALL: average scores across cognitive domains) **Panel B**: This panel shows that the post-flight decline in cognitive performance of SK was not transient. It persisted until the last post-flight measurement at R+180 (blue arrows). **Panel C**: This panel provides an overview of the number of subjects and the number of Cognition batteries that will contribute to the normative data-base for standard- (≤6 months) and long-duration (>6 months) missions.

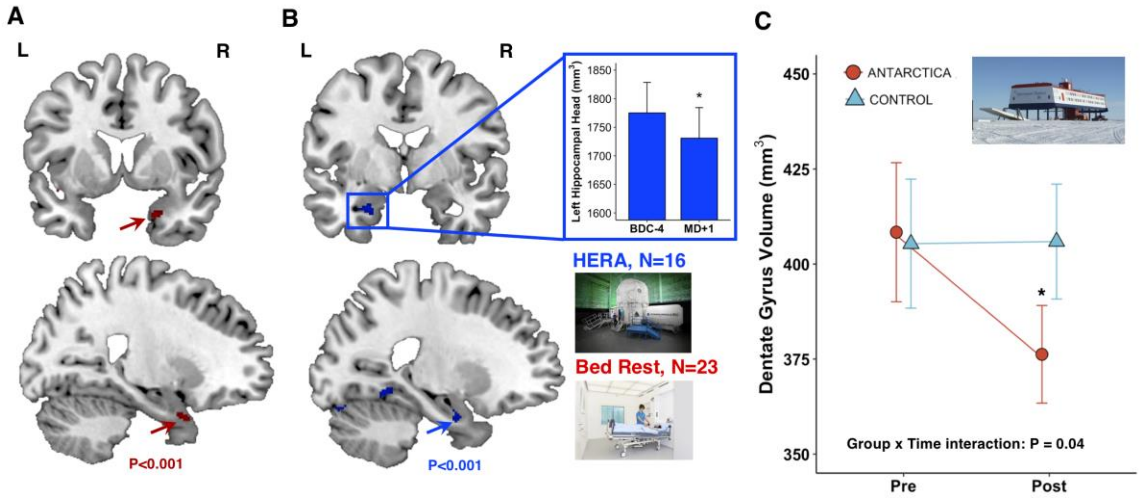


Figure 2: Panel A: Whole brain analyses using voxel-based morphometry showing the effects of 30 days of isolation in the NASA HERA habitat (blue, N=16, 7 women) and 60 days of head-down tilt bed rest (N=23 men). Both space analogs reveal a significant (P<0.001) decrease around the hippocampal head (anterior hippocampus) and the border of the amygdala. These data were confirmed by high-resolution imaging (see bar plot). **Panel B**: Individual and mean (±SE) age- and gender-adjusted in dentate gyrus volumes before and after long-duration overwintering (circles and triangle show women and men respectively). *P=0.023 for paired t-test. Mixed models including subject as random intercept confirmed a significant interaction (P=0.042) between time (pre vs. post) and group (Antarctic overwintering crew vs. control group). N=17 (8 winter-overs, 9 controls).

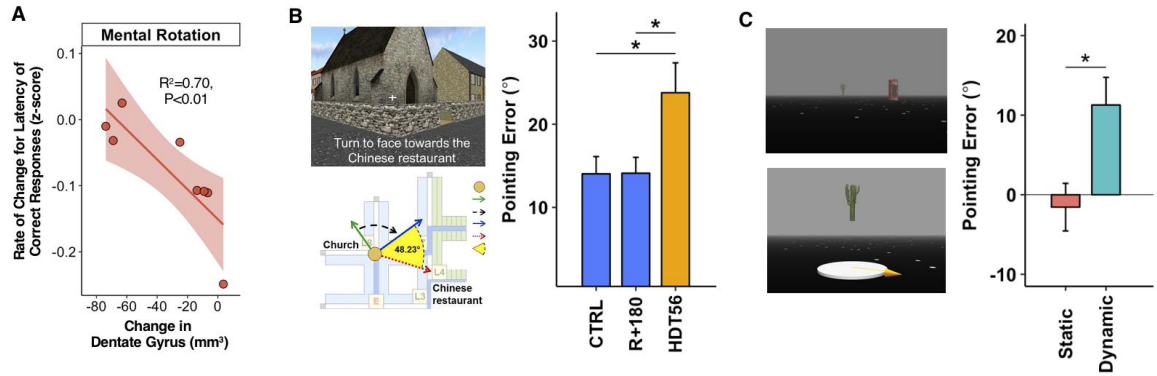


Figure 3: Panel A: Association between rate of change in visuospatial ability (mental rotation) and change in dentate gyrus volume. The rate of change in cognitive change was computed by regressing the monthly performance data (total of 10 time points per subject) during an Antarctic winter-over against time for each individual participant, respectively (N=8). Panel B, left: Example of a probe trial of the wayfinding task (cognitive mapping). After a route learning phase until 100% criterion, subjects were positioned in front of an object that they passed during the learning. They were then asked to point to another specific object that they encountered during their route learning. In the example shown here, the subject faces the front of the church, and

asked to turn himself toward the Chinese restaurant by virtually turning his position using the arrow keys of the computer. **Panel B, right**: Pointing error (difference between correct vector and subjective pointing) of wayfinding task after 56 days of bed rest compared to performance in a group of bed rest subjects after a recovery phase of 180 days and a group of gender- and age-matched controls (N=34, 11 bed rest subjects after 180 days, 11 bed rest subjects after 56 days of bed rest, 12 control subjects). *P=0.018 and P=0.019 compared to CTRL and R+180, respectively. **Panel A, left**: Example of spatial updating probe trial. During the encoding phase two objects are briefly shown on the screen. Once the objects disappear the participants experiences either a virtual translation (dynamic condition) or remains in his position (static condition), after which one of the two objects is shown again in the middle of the screen. Using a 3D-arrow the participant now has to move the arrow towards the original position of that object. **Panel A, right**: Effect of weightlessness on spatial updating performance. During each parabola, subjects performed two trials in 1g and 0g, respectively, for a total of 15 parabolas N=10 (4 women, 6 men), aged 33 to 50 years. The experiment was performed as part of the 66th ESA parabolic flight campaign. Data are mean (±SE) changes between 0g and 1g. Green refers to spatial updating trials, i.e. trials involving virtual forward movement. Red shows control trial, i.e. no translation. *P=0.028.

2.1 Level of Risk and Medical Monitor

a) What is this study's level of risk?

__X__Minimal
_____Greater Than Minimal

If different parts of the study have different levels of risk, please briefly outline the risks associated with each part in this protocol and consent form. Please note that the use of human research genetic testing is considered greater than minimal risk.

b) What is this study's Medical Monitor level?

_____Level 1
_____Level 2
_____Level 3
__X__Level 4
_____Not Required

If not required, please explain.

2.2 Study Summary

a) Expected Start Date:

7/1/2019 (Definition Phase)

1/1/2020 (Project Phase)

b) Expected End Date:

12/31/2019 (Definition Phase)

12/31/2026 (Project Phase)

c) Type of Subjects (please mark all that apply):

__X__Astronaut (US)

__X__Astronaut (CSA)

__X__Astronaut (ESA)

__X__Astronaut (JAXA)

_____Cosmonaut

__X__Non-Astronaut

2.3 Study Location(s): Identify the NASA location(s) where research procedures, including data collection and storage, will be performed.
Johnson Space Center, Clear Lake, TX
UTMB Victory Lakes, League City, TX

2.4 Other Sites/Institution(s): Please list any non-NASA sites or institutions where research procedures, including data collection and storage, will be performed.
University of Pennsylvania, Philadelphia, PA (data analysis and storage)
Charité Berlin, Germany (data analysis and storage)

3.0 Specific Aims and Hypothesis

a) Specific Aims:

This study consists of two projects:
Project A: Neurostructural and Cognitive Changes During Long Duration Low-Earth Orbit Missions: Cognition (PI Basner)
Project B: Spatial Cognition and Hippocampal Plasticity During Long-Duration Low-Earth Orbit Missions: HypoCampus in i1YMP (PI Stahn)
This study has the following specific aims:

- Specific Aim A1: Effects of Long-Duration Low-Earth Orbit Missions on Cognition performance
- Specific Aim A2: Normative Cognitive Performance Data as a Baseline for Future Long-Duration Missions
- Specific Aim A3: Brain Structural, Functional and Connectivity Substrates of Changes in Cognitive Performance Induced by Long-Duration Low-Earth Orbit Missions

- Specific Aim B1: Visuospatial Brain Domain Changes Induced by Low-Earth Orbit Missions
- Specific Aim B2: Effects of Long-Duration Low-Earth Orbit Missions on Visuo-Spatial Cognition
- Specific Aim B3: Biological Basis of Neurocognitive Changes During Low-Earth Or-bit Missions

b) Hypothesis(es): In line with the solicitation, the study is considered a non-inferiority trial. Accordingly, our aim is to show that the effects of the 1-year mission are not worse, i.e. non-inferior to the standard space missions of 6-month duration (applies to Specific Aims A1, A3, B1, B2, and B3 above). For Specific Aim A2, we will generate a normative database that can serve as a baseline for future long-duration missions. The 10 year-long astronauts will be the basis for this data-base, which will be augmented with existing data from 5 astronauts on 6-month missions and with Scott Kelly's data from his one-year mission. Importantly, we already collected Cognition data in N=86 astronaut surrogate subjects spending >6 months in space analog environments (3 Antarctic research stations and HI-SEAS). These data will be contrasted to the in-flight data and, if comparable, used to augment the normative database for LDM. We continue to collect data at Neumayer station in two NASA-funded projects, and will have up to 27 more subjects available for potential inclusion in the database by the end of this project.

c) Primary Outcome Measure: (Dependent Variables)
Specific Aim A1: Cognitive efficiency across domains as determined with the Cognition test battery
Specific Aim A3: fMRI local task activation while performing the MRI version of Cognition in the scanner
Specific Aim B1: Accuracy and reaction times for each cognitive task as determined with the Spatial Cognition test batteries
Specific Aim B2: Structural brain changes and local task activation while performing visuospatial tasks in the scanner
Specific Aim B3: BDNF, IGF-1, VEGF, Oxytocin (IL-1, IL-1ra, IL-10, TNFa)

d) Statistical Analysis: To assess the effect of spaceflight we will employ mixed-model analyses with time and group (control vs. spaceflight) and mission length as fixed factors and subjects as random factors. Significant main effects for variables will be followed-up using sequentially rejective multiple contrasts. To assess the relationships between several predictors and the primary outcomes, regression analyses such as ridge, lasso, and elastic net regression will be considered to minimize any problems associated with overfitting. To identify the relationship between changes, within-subject correlations, accounting for non-independence among observations using analysis of co-variance (ANCOVA) and statistically adjust for inter-individual variability will be used.

3.1 Study Design Characteristics

Sample Size: This study will include N=10 astronauts on 12-month missions, N=10 astronauts on 6-month missions, and N=10 astronauts on 2-month missions. These sample sizes were set by NASA. In line with the solicitation, the study is considered a non-inferiority trial. Accordingly, our aim is to show that the effects of the 1-year mission are not worse, i.e. non-inferior to the standard space missions of 6-month duration. For Project A, existing Cognition data from 6 astronauts on 6-month or 12-month ISS missions were used to determine the statistical power to demonstrate non-inferiority of cognitive efficiency across domains in the 12-month crew (expected N=11, including data from 1 existing astronaut) relative to the 6-month crew (expected N=15) for non-inferiority margins (NIM) of 0.2, 0.25, and 0.3 SD, when, in-fact, there is no performance difference. By sampling repeatedly in-flight, we increase precision for individual astronauts, which stabilizes variance across astronauts and thus increases statistical power. The analyses show that we expect to have >80% power (at α=0.05) to demonstrate non-inferiority with an a priori defined NIM of 0.25 standard deviations for ≥2 in-flight tests (we plan to acquire 6 and 5 tests in-flight during months 1-6 and 7-12, respectively). Should the performance of the 12-month crew be 0.05 SD (20% of 0.25 SD NIM) lower compared to the 6-month crew, we still expect to have >70% power to determine non-inferiority at a NIM of 0.25 SD. For Project B, the primary endpoint will be hippocampal subfield volume measured using a high-resolution brain MRI scan. The standard deviation is anticipated to be 50 mm^3. Assuming N=10 for each group (i.e. 6-month missions and 1-year missions), a type I error rate of 5% and that the true mean difference between missions is thought to be zero, we expect to achieve >80% for showing non-inferiority with a margin of >55mm^3. Considering a true difference of 5 mm^3 between 6-months and 1-year missions, corresponding to 10% of the non-inferiority limit, will still have >70% power to determine non-inferiority of 1-year missions.

4.0 Study Procedures, Tests, Evaluation

a) Study Procedures, Tests, and Evaluations: Please list, in sequence, all study procedures, tests, and evaluations required for the study.

(1) Brain-MRI

In order to examine both structural and functional brain changes associated with spaceflight, the MRI scanning of the brain shall include the following scanning sequences (depending on the scanner, software, and timing, the protocol can be slightly adapted accordingly):

Structural MRI measures will provide detailed information about anatomical features of the brain and allow us to monitor changes in an individual's brain structure. Functional MRI will provide information about brain function and allow for the measurement of individual differences in brain performance during challenging cognitive tasks.

Structural MRI:

- Field Map (Projects A&B)
- Whole brain T1-weighted MPRAGE anatomical sequence (Projects A&B)
- Whole brain T2-weighted SPACE anatomical sequence (Project A)
- Proton density weighted sequence for a high-resolution image of the hippocampus (Project B)
- T1-weighted fast spin echo locus coeruleus sequence (Project B)

Functional MRI:

- Whole brain resting BOLD MRI sequence (Projects A&B)
- Whole brain perfusion sequence (Project A)
- Whole brain task BOLD sequence - fCognition (Project A)
- Whole brain visuo-spatial task BOLD sequences (Project B)

During all MRI scans, subjects shall lie in a supine position with their eyes opened or closed based on task demands. Functional MRI scans may require subject responses to visual stimuli (tasks) using an MRI safe response box while lying in the scanner.

Prior to imaging, subjects will be required to complete specific surveys assessing subject eligibility to perform MRI scanning, and a questionnaire assessing their handedness.

(2) Cognitive Performance

Project A:

Cognition

Astronauts with perform NASA's Cognition test battery (10 neuropsychological tests always performed in the same sequence) according to the schedule below (see 4.0 d). Some of the tests are shared with NASA's Standard Measures project. A detailed description of the Cognition test battery can be found in Basner, M., et al. (2015). "Development and validation of the Cognition test battery " Aerospace Medicine and Human Performance 86(11): 942-952.

Project B:

Spatial Cognition

Astronauts will perform a set of cognitive tests specifically targeting spatial learning and memory and navigation. The test batteries will be divided into:

- **Spatial Cognition Test Battery 1:** includes the computerized tests and surveys to be applied both during ground and inflight sessions.
- **Spatial Cognition Test Battery 2:** includes the computerized tests and surveys to be applied during ground sessions only.

Outside of the test batteries, a **survey assessing the level of computer experience** will also be requested on-ground. It shall take place only once and it can be filled out any time during the pre-flight period.

When performing the tests or filling out the surveys, the subject shall not interrupt the test or survey but can stop for short periods in between tests and surveys.

For ground sessions: The test batteries shall be performed with the computer in seated position, at room temperature, preferably in a quiet room. Headphones may be used not only for noise cancelling purposes, but also in case specific instructions need to be provided during test batteries. On-ground, one of the tasks – Navigation Search – will not only be performed in seated position with the computer, but also in standing position with a head-mounted display with controllers (see Table 1). During this task, subjects will move freely within a circular area (about 4 m diameter).

For inflight sessions: In order to keep cognitive testing standardized between the ground and in-flight sessions, the Test Battery shall be performed with the computer in a fixed position. There is no special requirement on how the subject shall be fixed, providing that the subject is comfortable, not free floating and, preferably, in a quiet environment. Headphones may be used not only for noise cancelling purposes, but also in case specific instructions need to be provided during test batteries.

Table 1 provides an overview of the Test Batteries 1 and 2 compositions and in which sessions they shall be applied.

Table 1: *Test Batteries 1 and 2 composition and definition. It does not include the level of computer experience survey, as this will be filled in only once, outside the test batteries.*

Test Battery 1 & 2	
Visual Analogue Scales (VAS)	*Purpose*: To assess mood, fatigue and sleep *Description*: To assess mood, fatigue and sleep, affective states, visual analogue scales (VAS) will be used.
Test Battery 1	
Spatial Updating	*Purpose:* To assess spatial updating *Description*: Subjects initially have to encode the position of an object presented at unpredictable positions in a virtual environment. The object then gradually disappears, followed by a static or dynamic delay phase. In the dynamic delay phase subjects experience a virtual forward translation and rotation, after which subjects have to point toward the remembered location of the object. In contrast, in the static delay phase they remain stationary instead of moving forward, thus requiring them to point toward the original location of the target object at retrieval. *Publication*: *Nat Neurosci* 11, 1223-1230 (2008)
Four Mountains Task	*Purpose:* To assess topographical memory *Description*: To specifically target topographical memory, a version of the Four Mountains Task will be performed. Subjects will be asked to briefly study a landscape scene. Subsequently, they will be shown several variations of the previously displayed scene from a novel viewpoint and under altered non-spatial conditions and they have to identify, which of these scenes is identical to the one that was initially presented. *Publication*: *Front Hum Neurosci* 6**,** 338 (2012).
Point to Origin Task	*Purpose*: To assess path integration *Description*: A sparse visual flow is presented on a screen to the subjects, and supported by auditory information. At the end of each path, subjects will be asked to point back to the origin by rotating an arrow. In addition, they will also have to estimate the distance of the homing vector (linear distance to the point of origin). After each trial, subjects will be asked to rate the level of difficulty of the trial. *Publication: J Exp Psyc: Human Perception and Performance 31, 1199 (2005); Sci Rep 5, 11426 (2015).*
Navigation Search	*Purpose:* To assess spatial memory and spatial updating *Description:* Subjects will be shown a virtual environment that contains a number of boxes. Some of the boxes contain a target, which can only be seen when the box is approached from the front to a close distance. The task is to locate and collect all targets as quickly as possible. Each session the task will be performed in two different conditions, differing in their background (night vs. day). On-ground the task will also be administered with a head mounted display and controllers, while moving in a small circular area (radius: 4 m).

Test Battery 2	
Perspective Taking	*Purpose*: To assess spatial orientation ability, i.e. the ability to occupy new imaginary positions within a configuration of objects *Description*: A picture with several objects is displayed on a screen. On each item, the subject is asked to imagine being at the position of one object in the display (the station point) facing another object (defining their imagined heading or perspective within the array) and is asked to indicate the direction to a third (target) object. *Publication*: *Intelligence 32, 175-191 (2004)*
Virtual Mazes	*Purpose*: To assess spatial navigation *Description*: This test comprises several tasks. During each task a 3D environment is presented to the subject from a first-person perspective. The subject is then asked to move to a target using different cues, starting from different positions as quickly as possible. Subjects may perform variations of this task during preflight- and postflight testing, including different environments and set ups, and complete questions about their strategies. *Publication*: *Hum Brain Mapp 36, 1265-1277 (2015); Frontiers in aging neuroscience 4, (2012); Neurobiol Learn Mem 117, 42-50 (2015)*
Cognitive Mapping Task	*Purpose:* To assess spatial memory formation *Description*: Subjects will be asked to first learn a route through a novel virtual large realistic environment, consisting of a network of paths, non-specific buildings, and distinctive landmarks. They are instructed that they are required to learn a long, indirect route through the environment and will be asked to provide directions during a subsequent probe trial. Following the completion of the learning phase, subjects will be asked to perform a cognitive map test by indicating spatial relationships between two specific landmarks encountered along the route during the learning phase. Importantly, the target landmark is never visible from the respective trial location. The pointing error between the correct direction and estimated direction between the current location and the target landmark will be used to quantify spatial memory. After completion of the task subjects will perform a debriefing questionnaire about their sense of direction and a survey about their response strategies. Subjects may perform variations of this task pre- and postflight. *Publication*: *Hippocampus 26, 185-193 (2016)*

(3) Biospecimen

Project B:

Venous Blood Collection

A total of 7.5 ml of blood shall be collected in fasting state (water is allowed) following standard procedures. After blood collection the blood samples shall be centrifuged and moved to on-orbit cold stowage.

Scheduling and session constraints

- No EVA, EVA training or physical exercise 12 hours prior to start of blood collection, cognitive testing and MRI

- In-flight, no sleep shifting of more than 2 hours three days prior to data collections, and no time shifting of 6 or more hours one week prior to data collections (for each hour of sleep shifting, one day should pass between the actual time shift and the start of cognitive testing and neuroimaging). For ground sessions, the sleep shift requirements can be relaxed as needed to fit the crew's schedule constraints, but the deviation should be kept to the minimum possible.
- Blood collection in fasting state (water is allowed).
- It is recommended that subjects void immediately prior to cognitive testing and neuroimaging to avoid interruption of these activities due to visit to the toilet.
- No caffeine consumption 4 hrs prior to blood collection, cognitive testing and MRI.
- No alcohol consumption 12 hrs prior to blood collection, cognitive testing and MRI.
- Ideally, no other cognitive testing (i.e., tests not related to this experiment) should be scheduled on the day of cognitive testing or neuroimaging sessions. If this is not possible, deviations to the above requirement shall be coordinated with the project PIs on a case by case basis.
- fMRI, MRI & Spatial Cognition must be at least 24 hours after Gadolinium and/or Dotarem contrast application
- No Nitroglycerin, Aminophylline or Proparacaine use within 8 hours prior to Cognition or Spatial Cognition.
- fMRI, MRI & Spatial Cognition either before or at least 24 hours after administration of Fluorescein, Definity, LexiScan or Omnipaque. No Fluorescein, Definity, LexiScan or Omnipaque use within 8 hours prior to Cognition or Spatial Cognition.
- fMRI, MRI, Spatial Cognition, and Cognition must be done before dilation of the eye with Tropicamide, Phenylephrine or other dilating eye drops if on same day.

b) Will subjects or their health care provider be given the results of any experimental tests that are performed for the study? Yes____ No __ X___

If "yes", please describe the tests, provide a rationale for providing subjects with the experimental test results and explain what, how and by whom subjects and their health care provider will be told about the meaning, reliability, and applicability of the test results for health care decisions.

c) Will subjects undergo any study procedures or tests off-site? Yes __X__ No____
fMRI scans will be performed at UTMB's Victory Lakes scanning facility.

d) Time commitment: Indicate how much time will be required of the subjects, both per visit and in total, for the study. Do not include time spent passively, such as periods when a monitoring device is worn, but no special activity is required.

Project A time commitment:

Preflight Test/Activity	Schedule	Crew Time (min)		Post-flight Test/Activity	Schedule	Crew Time (min)	
		per session	total			per session	total
Cognition familiarization	*L-180**	*60*	*60*	*Cognition debrief*	*R+95*	*30*	*30*
Cognition	*L-180, L-120**	*30*	*60*	*Cognition*	*R+6*, R+30*, R+90, R+180, R+360*	*30*	*150*
Cognition with fMRI Cognition familiarization	*L-60*	*45*	*45*				
Combined fMRI with Cognition (Project A) and MRI Spatial Cognition (Project B)	*L-59*	*90⁺*	*90⁺*	*Combined fMRI with Cognition (Project A) and MRI Spatial Cognition (Project B)*	*R+1-7, R+30*	*90⁺*	*180*
**shared with ISS Crew Standard Measures project ⁺shared with Project B, total scan time 180 min*							
TOTAL PREFLIGHT BDC (per subject)			***255***	**TOTAL POSTFLIGHT BDC (per subject)**			***360***

Test/Activity	Schedule	Crew time (min)	
		per session	total
Cognition (1 month crew)	*R-14**	*30*	*30*
Cognition (2 month crew)	*FD 15-30*, R-14**	*30*	*60*
Cognition (6 months crew)	*FD 15-30*, 60, 120, R-14* (reserve sessions @ FD 90 and FD 150)*	*30*	*120 (to 180)*
Cognition (12 months crew)	*FD 15-30*, 60, 120, 180*, 240, 300, R-14* (reserve sessions @ FD 90, 150, 210, 270, 330)*	*30*	*210 (to 360)*
TOTAL IN-FLIGHT CREW TIME (per subject): 1-month crew			***30***
TOTAL IN-FLIGHT CREW TIME (per subject): 2-months crew			***60***
TOTAL IN-FLIGHT CREW TIME (per subject): 6-months crew			***120 (to 180)***

TOTAL IN-FLIGHT CREW TIME (per subject): 12-months crew	***210 (to 360)***
**shared with ISS Crew Standard Measures project*	

Project B time commitment:

Preflight Test/Activity	Schedule	Crew Time (min)		Post-flight Test/Activity	Schedule	Crew Time (min)	
		per session	total			per session	total
Spatial Cognition Familiarization	*L-180*	*90*	*90*				
Spatial Cognition Test Battery I	*L-180, L-60*	*60*	*120*	*Spatial Cognition Test Battery I*	*R+6, R+30, R+180, R+360*	*60*	*240*
Spatial Cognition Test Battery II	*L-179, L-59*	*90*	*180*	*Spatial Cognition Test Battery II*	*R+6, R+31, R+181, R+361*	*90*	*360*
MRI Spatial Cognition (Project B)	*L-179*	*130*	*130*	*MRI Spatial Cognition (Project B)*	*R+181, R+361*	*130*	*260*
Combined fMRI with Cognition (Project A) and MRI Spatial Cognition (Project B)	*L-59*	*90+*	*90+*	*Combined fMRI with Cognition (Project A) and MRI Spatial Cognition (Project B)*	*R+1-7, R+30*	*90+ (95 on R+1-7)*	*185*
Blood draw	*L-180, L-60*	*15*	*30*	*Blood draw*	*R+5, R+30, R+180, R+360*	*15*	*60*
+shared with Project A, total scan time 180 min; R+1-7 includes additional 5 min for re-familiarization with the MRI protocol (total of 185 min)							
TOTAL PREFLIGHT BDC (per subject)			***640***	**TOTAL POSTFLIGHT BDC (per subject)**			***1105***

Test/Activity	Schedule	Crew time (min)	
		per session	total
Spatial Cognition (1 month crew)	*R-14*	*60*	*60*
Blood Draw (1 month crew)	*R-14 (time covered by other experiments)*	*85*	*85*
Spatial Cognition (2 months crew)	*FD 15-30, R-14*	*60*	*120*
Blood Draw (2 months crew)	*FD 15-30, R-14 (time covered by other experiments)*	*85*	*170*
Spatial Cognition (6 months crew)	*FD 15-30, 60, 120, R-14*	*60*	*240*

Blood Draw (6 months crew)	*FD 15-30, 60, 120, R-14 (time covered by other experiments)*	*85*	*340*
Spatial Cognition (12 months crew)	*FD 15-30, 60, 120, 180, 240, 300, R-14*	*60*	*420*
Blood Draw (12 months crew)	*FD 15-30, 60, 120, 180, 240, 300, R-14 (time covered by other experiments)*	*85*	*595*
TOTAL IN-FLIGHT CREW TIME (per subject): 1-month crew			***145***
TOTAL IN-FLIGHT CREW TIME (per subject): 2-months crew			***290***
TOTAL IN-FLIGHT CREW TIME (per subject): 6-months crew			***580***
TOTAL IN-FLIGHT CREW TIME (per subject): 12-months crew			***1015***

e) Facilities: Please provide a description of the facilities used in this research.
Pre/Post-flight:

- NASA Johnson Space Center, 2101 E NASA Pkwy, Houston, TX 77058, USA
- UTMB Health League City, 2240 Gulf Fwy S, League City, TX 77573, USA

f) Adequacy of Resources: Principal investigators must have the necessary resources required to conduct the proposed research in a way that assumes the rights and welfare of participants are adequately protected. Describe the resources you have in place to conduct this study. Examples may include personnel, funding, and equipment required to perform the study.

The principal investigators and their teams have all necessary resources to conduct the proposed research in a way that assumes the rights and welfare of participants are adequately protected. Adequate office space for data analysis is available at the University of Pennsylvania and Charité Berlin. Specific funding including personnel, hardware and traveling costs will be provided by NASA and the German Aerospace Agency (DLR).

g) Please provide/describe the test termination or withdrawal criteria guidelines and associated rationale.

- The subject experiences discomfort or pain that cannot be alleviated
- The subject voluntarily withdraws from the study
- The researcher believes that it is not in the best interest of the test subject to stay in the study
- There is any problem with following study related instructions
- There is any serious complication during the study
- There is inappropriate behavior
- The study is suspended or canceled
- The subject's information is or becomes unusable for any reason
- Events beyond NASA's control occur, for example: fire, explosion, disease, weather, floods, terrorism, wars, insurrection, civil strife, riots, government action, or failure of utilities

4.1 Equipment Used During Research

Unmodified, commercially available devices that are being used in accordance with their intended use and that are already FDA certified or CE marked as being MDD 93/42/EEC compliant do not require additional assessment. An exception to this is any device whose primary function is to radiate or store electrical, thermal, or mechanical energy during their operation. In this case, a safety assessment will be performed to determine the "suitability of intended use" and you could be contacted with a request for specific data.

Any device that is modified from the commercially available version, that will not be used in accordance with the manufacturers recommendations, or that has been designed and built for research purposes will require an additional assessment.

Computers and other equipment used to collect and process your data do not need to be listed however software used to control potentially hazardous test operations should be identified and is subject to review.

Any device that will be in electrical contact with the research subject must show compliance with ANSI/AAMI ES1-1993, *Safe Current Limits for Electromedical Apparatus*.

a) Having read the above statements, will any equipment be used during research (i.e., for retrospective studies answer "No")? Yes ____ No__X__

If “no”, then continue to the next numbered section. If “yes”, then answering (b) and (d) are required.

b) Are all of the devices that you are using in this research:

1. **Unmodified and commercially available**
2. **Used in accordance with manufacturers recommendations**
3. **FDA certified or CE marked as being MDD 93/42/EEC**
   Has been previously reviewed by the NASA JSC Test Safety Office

   Yes ____No____

   If “yes”**,** skip to (d). If “no”, provide the common name for each device and include the manufacturer and the model number of your specific device(s).

c) For each of the devices listed in 4.1 (b) attach the following additional information so that a safety assessment may be performed. Please attach supporting documentation to the Local Site Documents section.

1. A description of any hardware modifications that have been made to commercially available equipment. Explain how these modifications have not modified the safety of the hardware. Attach design data as required to support these statements.
2. A description of how operations that are not in accordance with the manufacturers recommendations will not affect the research subject safety.
3. Hardware that is not commercially available or that has been built only to support research requires additional information.

For electronic equipment include a:

- block diagram
- detailed schematic
- description of circuit operations
- description and test data for software that controls critical functions For mechanical devices include:
- detailed design data
- structural or loads analysis showing factors of safety

Research Device Information Documents

Research Device Document Description Date Created Date Modified
There are no items to display

d) Is the primary function of any of the devices used in your protocol to radiate or store electrical, thermal, or mechanical energy that could come into contact with the research subject during their operation? Include devices even if they are FDA certified or MDD 93/42/EEC complaint and CE marked. Do not include radiographic imaging or ultrasound hardware.

Yes____ No__ X__

If "yes", provide the common name for each device and include the manufacturer and the model number of your specific device(s). You will be contacted with a request for specific data if required.

5.0 Remuneration Payment to Participants

Will any subjects receive remuneration for study participation? Yes__X__ No____

If "yes", please describe the remunerations subjects will receive and in what form. Control subjects will be numerated according to standard policies for participation suggested by FAP/BHP and/or ESA/DLR Standard policies, if applicable.

5.1 Costs Related to Participation

a) Select all categories indicating costs which participants or their insurance companies will be responsible for:

__X__Participants will have no costs associated with this study
____Study Related procedures
____Study Drugs or Devices
____Other

b) If study participants or insurance companies will assume any costs for this study, describe the procedures, drugs, or devices for which the participants or their insurance companies must assume costs:

N/A

5.2 Study Population

a) General description of the study population:
Astronauts participating in ~1 to 2 month, 6-month, and 12-month duration space missions. Subjects participating in the ground control experiment will be matched for age, sex, and educational background, but must not necessarily be astronauts.

b) Target number of non-astronaut participants:
30

c) Target number of astronaut participants:
30

d) Does this investigation have an open ended study population? Yes____ No__X__
If "yes", please describe the rationale for an open ended population.

e) Please list the inclusion and exclusion criteria for enrollment of normal, healthy volunteers (Non-Astronauts) and, if applicable, astronauts :

1. Subjects who do not comply with the mission duration (Refer to 3.2 b))
2. Subjects that do not comply with the MRI testing requirements. The following conditions may exclude the subject from MRI scanning or require additional examination to assess specific contraindications:

- Tinnitus;
- Sensori-neural hearing loss > 30 dB;
- Pace-maker or internal defibrillator;
- metallic implants (e.g. orthopedic plates after bone fractures, joint replacements, surgical staples or clips, artificial heart valves, stents, cava filters);
- Metallic splinters (e.g. after an accident or due to war injury);
- Non-removable dental brace;
- Intrauterine contraceptive device;
- Cochlear implant (implanted hearing device);
- Medication pump;
- Acupuncture needle;
- Other foreign bodies/objects which are non-removable;
- Pregnancy (or its possibility);
- Previous brain and/or heart surgery.
- Tattoos and/or permanent make-up in the body (some inks contain metallic particles).

f) If pregnant women are excluded from participation please provide a justification:

Female subjects in this study are either astronauts or will model those in the astronaut population for whom participation in space missions is not allowed during pregnancy.

g) If there are any age, ethnic, language, or gender-based exclusion criteria, please provide justification. Additionally, if women of child-bearing potential are to be excluded please provide a scientific or medical justification for their exclusion:

Female subjects in this study are either astronauts or will model those in the astronaut population for whom participation in space missions is not allowed during pregnancy.

5.3 Risk Assessment

a) Please describe the risks associated with this study :

(Women of child-bearing potential or pregnant women: If your study includes pregnant subjects and/or women of child-bearing potential please include the risks to pregnant females and fetuses. If there are currently no known risks please add the following statement "Currently there are no known risks to a pregnant female and a fetus for this protocol. However, unknown adverse fetal events may occur, even in the absence of maternal symptoms.")

(1) Risk associated with exposure to strong magnetic field.

(2) Risk of a metallic object flying through the air toward the MRI magnet and hitting a person.

(3) Risk of an unexpected abnormality being observed in a specific subject's MRI even though scans are not intended for diagnostic purposes. These abnormalities are termed "incidental findings."

(4) Risk associated with feeling uncomfortable or claustrophobic while inside the MRI magnet.

(5) Loud noise while in MRI scanner.

(6) There is the potential that subjects may develop a headache or motion sickness and/or experience stress during cognitive testing due to the amount of computer work and/or moving in 3D environments.

(7) There may be some discomfort associated with the collection of the blood samples, including possible bruising of the arm, redness, swelling around the site, bleeding at the site, dizziness, fainting, sweating, coldness of skin, numbness and tingling of hands and feet, nausea, vomiting, possible visual disturbance, syncope and injury fall from fainting. In some cases, more than one venipuncture may be necessary. Rare adverse effects include thrombosis of the vein due to trauma and infection which results in thrombophlebitis.

b) Please describe how you are going to minimize the risks:

(1) The levels of energy used to perform magnetic resonance measurements are far less than are used in a X ray, and many patients have been safely studied using magnetic resonance techniques. Subjects will also undergo a checklist before entering the MRI room to verify that they do not have anything harmful in or on their body.

(2) We require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once subjects are in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet room.

(3) Most incidental findings have no significant health consequences, but in a small percentage of cases further evaluation or treatment may be indicated. If an incidental finding is noted in a subject's MRI data, the subject will be notified and given a written report describing it. It will then be up to the subject to pursue it with his/her physician. Although study personnel may be able to provide some advice, the decision of whether and how to pursue an incidental finding can only be made by the subject's physician who has knowledge of the subject's medical history.

(4) If a subject becomes uncomfortable inside the magnet, the subject may withdraw immediately from the study. They will be able to talk to the operator throughout the study via intercom, and will be able to let us know right away if they want to stop the study and get out of the scanner.

(5) Participants will wear foam earplugs and / or headphones to reduce the loud noises made by the scanner.

(6) If subjects feel upset and emotional discomfort while participating in the study, subjects may contact the PI. Should they feel that they are unable to complete the task during the course of the study, they are free to withdraw their consent to participate in this experiment.

(7) Sterile disposable hardware will be used for all blood drawing procedures. In the event of fainting during the blood draw, a medical evaluation will be performed. Food and drink will be available.

c) Has a hazard analysis been done? Yes__X__ No_____

If “yes”, please attach the documentation of the analysis.

5.4 Potential Benefits and Alternatives

a) Are there potential direct benefits to study subjects? Yes_____ No__X___

If “yes”, please describe any potential for direct benefits to participants in this study

b) Please describe any potential benefits to Society or Space Flight:

There is no direct benefit to subjects. However, given the neurocognitive functions required for effective performance in space, our knowledge on how humans will cope with living for prolonged periods of time in an ICE environment is extremely limited (only 4 humans have spent consecutively more than 1 year in space). The

data we propose to collect will, for the first time, reliably demonstrate whether prolonging mission duration to one year will have detrimental effects on general cognitive performance, spatial cognition and hippocampal plasticity relative to the shorter 6-month and 2-month missions.

c) Please describe any alternatives to study participation available to prospective subjects:
Choose not to participate

6.0 Privacy & Data Confidentiality

Subject privacy and data confidentiality must be maintained in accordance with 1) NASA Policy Directive (NPD) 7100.8, "Protection of Human Research Subjects"; 2) NASA Procedural Requirements (NPR) 7100.1A, "Protection of Human Research Subjects"; and 3) to the extent allowed by Federal law.

a) Please select all data types that will be collected: (check all that apply)

___X___Name
___X___Age
___X___Gender
___X___Race
_____Full Face Photographic Image
_____Full or partial Social Security Number
___X___Telephone number
___X___Email Address
___X___Mission
___X___Relative Day
___X___Space Flight Duration
___X___Crew Position
___X___Other, please specify: Neurobehavioral / psychological data, biochemical data, neuroimaging data.

This study is part of a complement of interrelated studies that will be implemented as one study.

This specific investigation is requesting data from the following other investigations in this complement or from other experiments collecting as defined in the crew's individual Data Sharing Plans:

Standard Measures (Pro2231, PI: Clement):

- Cognition
- Blood (Insulin-like growth factor 1, Vascular endothelial growth factor)
- Cellular profile

- Actigraphy
- Biochemical Markers
- Microbiome
- Sleep
- Sensorimotor

NINSCAN (STUDY00000247, PI: Zhang):

- Blood (Brain-derived neurotrophic factor)

This specific investigation is also requesting the following from Medical Operations (MEDB):

- T1 and T2 weighted structural scans, DTI Sequence (Med Ops MRI, MEDB 1.10)
- WinSCAT (Med Ops, MEDB 7.4)
- Radiation - Personal Dosimetry (Med Ops, MEDB 3.1)
- Exercise Logs (Med Ops, ASCR Exercise, MEDB5.2)
- Medication Logs (Med Ops, MEDB 1.1/1.3)
- Clinical Lab Assessment (Med Ops, MEDB 2.1)
- Physical Fitness Evaluation: Functional Fitness (Med Ops, MEDB 5.1)
- Cycle Ergometer/Aerobic Functional Capacity (Med Ops, MEDBN 3.07)

This specific investigation is also requesting the following Environmental/ECLSS variables:

- CO_2 Levels
- Radiation - Station Level
- Ambient Temperature
- Humidity
- Air Pressure
- O_2 Levels

This specific investigation is also requesting the blood draw spreadsheet and the timeline from day before until end of each session from ROI.

b) How will the data and/or biospecimens for this study be collected, recorded, and by whom?

Specific Aims A3 and B1: Neuroimaging will be performed using a 3T Siemens scanner equipped with a head coil and a projection system. A laptop, running Presentation® (Neurobehavioral Systems, Inc., Berkeley, CA, USA) and in-house developed software and an MRI-compatible response box (Lumina, Cedrus Corporation, San Pedro, CA, USA/Current Designs Inc., Philadelphia, PA, USA).

Specific Aims A1, A2, and B2: Cognitive Performance. The Cognition battery will be administered with calibrated laptops at JSC and on the ISS. Cognitive tests and VAS will be administered using laptops and/or iPads, running executable files provided by the science team. Responses shall be logged using the keyboard and/or a standard joystick. During on-ground testing, some tests will not only be executed using a laptop, but it will also be administered via head mounted display with controllers (e.g., HTC Vive).

Specific Aims B3: Blood draws are obtained via venipuncture using standard blood collection equipment will be employed. After collection samples will be immediately centrifuged for 10 min and then aliquoted in up to 10 tubes of 250 microL each. All samples will be stored at –80°C (–68°C to –100°C).

The data will be collected by the Co-PIs Dr. Basner (Specific Aims A1-3) and Dr. Stahn (Specific Aims B1-3) with the help of Dr. Stahn's team and the Behavioral Health and Performance Lab at JSC (Co-I Dr. Roma).

c) Select how data and/or biospecimens will be identified:

_____No identifiers will be obtained by the investigators.

__X__Identifiers are obtained. However, data is coded and an investigator has the code key.

d) Select how data and/or biospecimens will be stored (select all that apply):

___X__Data are kept in locked file cabinet

___X__Data are kept in locked office or suite

___X__Electronic data is encrypted and protected with a password

___X__Data are stored on a secure network

_____Biological samples are kept in a locked freezer

___X__Other, please specify:

Any paper records generated for this investigation will be coded using non-attributable codes. Such records will be stored in locked filing cabinets and in locked rooms. Electronic records for this investigation also will be coded using the non-attributable codes. Any electronic records will be stored on computers located in locked rooms in the offices. These computers are password protected and meet the information technology security requirements. If Internet connection is available, encrypted data will be transmitted to secure servers.

e) Please describe the encryption method employed to protect the data.

All cognitive test and neuroimaging data will be encrypted. The Cognition database is maintained and operated by Penn Medicine Academic Computing Services (PMACS) on their secure servers. User authentication to the central database is implemented using the password hashing algorithm described in RFC 2898,

recommended for use by federal agencies. The encryption method we use to protect the data while "in-motion" to the server is a 256-bit AES (Advanced Encryption Standard) encryption algorithm. Any identifiable information will be stripped from all data sets and will only be accessible by the Co-PIs or their designee. The electronic data is de-identified and encrypted automatically at the time of collection. Only the Principle Investigator or his designee will be able to access the data.

f) Please describe the authentication methods use to ensure the security of the database.

To validate the identity of data users and prevent unauthorized access, all hard drives and each file will be protected using password-based authentication and the following requirements: The password must (i) not contain significant parts of the user name, first name and/or last name of the user, (ii) have at least 8 characters and (iii) contain three out of the following four categories: capital letters, small letters, numbers, and symbols.

g) Who, other than the specified study team, will have access to the study records or data? Specify their name, role, and affiliation.

None.

h) How will the investigator maintain data privacy in the test setting(s)?

Testing is restricted to the subject and the test operators only, unless a subject gives permission for an observer to attend. Subjects will be pseudonymized. The coding sheet will be kept in a locked office. All data, including electronically stored data and hard copies will be labeled with the designated subject code. The coding sheet will be retained by the investigator team only and will not be released without his or her consent unless specifically required by law. Information extracted from medical records (if applicable) will be treated in the same fashion as data gathered during experimentation.

i) What are the consequences to participants of a loss of privacy (e.g., risks to reputation, insurability, and other social risks)?

The researchers of this study will do everything in their power to ensure the participant does not experience a loss of privacy from their participation in this study. This study collects data on current behavioral/psychological states, and brain structure and function. It includes a survey consisting of visual analog scales that ask the subjects to indicate when they went to bed and when they got up, and whether they a conflict within the past 3 days and if so if it was solved. In addition, it asks subjects to provide a rating between 0 and 100 on their sleep quality, fatigue, tiredness, exhaustion, stress, workload, happiness, sickness, motion sickness, depression and loneliness. Due to the small sample size, and especially for astronaut subjects in which other factors make it difficult to ensure non-attributability of the data, the loss of privacy could generally pose a risk to their reputation. However, given that these scales are not considered valid tools to diagnose any

neuropsychiatric disorders and/or any other diseases, and also assess states, but not traits, this risk is suggested to be minimal.

j) If coded or identified data will be released, specify the persons/agencies to whom the information will be released. Please also indicate the provisions that will be taken to assure that the transmission of the data will be maintained confidential:
Data will not be released to any persons other than those on the study team. In case any data needs to be transmitted, we use Transport Layer Security (TLS), Secure Socket Layers (SSL), or secure transfer protocol (sFTP) for sending and receiving files over the network.

k) When the study is completed and the data is submitted and accepted by NASA, please indicate your plans for the destruction of the local dataset.
De-identified data will be kept with the Co-PIs at the University of Pennsylvania and at Charité University Medicine Berlin, Germany.

l) Is this study collecting or using health information? Yes __X__No____

m) Describe any additional steps taken to assure that identities of subjects and any of their health information, which is protected under the law, is kept confidential. If photography, video or audio recordings will be made as part of the study, disposition of these recordings should be addressed here and in the consent form.
Any photo or video recordings taken will be treated as any other data from subjects and will be kept separately.

n) Please describe how data and biospecimens will be handled if a participant withdraws their consent.
The data will contribute to the specified analyses unless the participant explicitly asks that their data shall not be used this way.

7.0 Process of Consent

a) Describe when, where, and how potential participants will be recruited.
The consent process will be initiated at the JSC with an informed consent presentation to prospective study participants by the science team.

b) Describe how, when, and where the consent process and documentation will be completed.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make informed decisions about their participation in this study. In addition, the investigators will discuss all the study procedures with the subjects, and will make sure that all their questions are answered. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All aspects

of the protocol and procedures are disclosed to the subjects. Subjects' participation in this study is completely voluntary, and subjects may withdraw at any time without prejudice.

c) Who will obtain informed consent from participants for this protocol?

The Co-PIs or their designee will obtain consent.

d) Describe the consent withdrawal procedures

Study participants can contact the Co-PIs or their designees listed on the consent form at any time to withdraw from the study.

7.1 Drugs, Devices, Biologics, foods and dietary supplements

If no drugs, devices, biologics, foods or dietary supplements are being used please skip this section

a) Does the study specify the use of an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to diagnose, cure, treat, or mitigate a disease or condition?

Yes____ No__X__

If “yes”, please list name(s) here and complete the drug section of the eIRB smartform.

b) Does the study evaluate the safety or effectiveness of a device? Yes _____No__X__

If “yes”, please list name(s) and complete the device section of the eIRB smartform.

7.2 Data and Safety Monitoring Plan

a) Please provide a plan for data and safety monitoring for this study.

The study will be monitored only by the study investigators and/or sponsor, and without a formal Data Safety Monitoring Plan.

b) Describe the clinical criteria for withdrawing an individual subject from the study due to safety or toxicity concerns.

A subject will be withdrawn from the study if any contraindications for performing MRI scans should apply. Subjects will also be withdrawn from the study if any of the neurobehavioral measures should cause considerable discomfort (e.g. develop a

headache or motion sickness and/or feeling highly stressed), and potentially impair their well-being and performance.

c) Summarize any pre-specified criteria for stopping or changing the study protocol due to safety concerns.

Personal discomfort such as headaches, motion sickness and/or highly increased stress levels observed during cognitive testing, that lead to mood disturbances and performance impairments.