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Summary Report for the Technical Interchange Meeting: Optimization of Translational Animal Models to Assess Human Spaceflight Performance for Studying the In-Flight Effects of Space Radiation: The Journey to Mars and Back

Proceedings of a NASA-sponsored workshop held at the South Shore Harbour Resort & Conference Center, League City, TX on June 13 and 14, 2017

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Sponsored by NASA Human Research Program's Human Factors and Behavioral Performance Element, and Space Radiation Element

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Contents

Abbreviations/Acronyms

5C-CPT	5 choice continuous performance test
ASST	Attention set shift test (sometimes ATSET)
BAC	Blood alcohol concentration
BART	Balloon analog risk test
BMed	Behavioral medicine
CNS	Central nervous system
CBS	CNS/BMed/Sensory motor
DDF	Distant Dipolar Field nuclear magnetic resonance
DG	Dentate gyrus field of hippocampus
DSI	Diffusion Spectrum magnetic resonance imaging
EEG	Electroencephalography
ELISA	Enzyme-linked immunosorbent assay
FDG	Fluoro-deoxyglucose
fMRI	Functional magnetic resonance imaging
GCR	Galactic cosmic ray
HERA	Human exploration research analog
HFBP	Human Factors and Behavioral Performance
HHC	Human Health Countermeasures
HPA	Hypothalamic-pituitary-adrenal
HRP	Human Research Program
HZE	High charge (Z) energetic (E) particle
ICE	Isolation, confinement and environment
ISS	International Space Station
JSC	Johnson Space Center
MCCB	MATRICS consensus cognition battery (developed for schizophrenia research)
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance spectroscopy Imaging
NHP	Non-human primate
NIMH	National Institute of Mental Health
PEL	Permissible exposure limit
PET	Positron emission tomography
PI	Principal investigators
POL	Permissible outcome limit
PVT	Psychomotor vigilance
RDoC	Research Domain Criteria
rPVT	Rodent psychomotor vigilance test
SR	Space Radiation
SSRIs	Selective serotonin reuptake inhibitors
TBI	Traumatic Brain Injury
TIM	Technical Interchange Meeting
TSPO-PET	Translocator protein positron emission tomography
UCFlex	Unconstrained Cognitive Flexibility behavioral test
VOLT	Visual object learning test

Introduction

In addition to the musculoskeletal and sensorimotor changes that astronauts develop from exposure to microgravity, astronauts may also develop decrements in behavioral and psychological health from stressors that include sleep deprivation, circadian disturbances, isolation, confinement, and elevated CO_2 levels. NASA is actively engaged in assessing astronauts' health and performance to manage these risks on the International Space Station (ISS), and to develop additional mitigations strategies for future long-duration exploration missions. Spaceflight exploration missions will present much greater challenges to crewmembers' behavioral health and performance than those currently faced by astronauts working and living in the ISS because deep space missions will include unprecedented duration, distance, isolation, and confinement under increasingly autonomous operations, along with greater exposure to the space radiation environment beyond low-Earth orbit.

Psychologists and psychiatrists support the astronauts' behavioral health using a suite of behavioral and cognitive assessment methods that have been adapted for use in space to assess a number of psychological and neuropsychological domains. These assessment tools have also been used in ground-based research studies to detect impairments due to circadian and sleep disturbances, and the effects of isolation and confinement in spaceflight analogs. It is important to recognize that astronauts are a unique population of individuals with high-functioning cognitive abilities, who are in exceptionally good health, and that their performance is being evaluated in a unique environment.

Although many performance measures can be directly assessed in humans, NASA must rely on animal models to evaluate the potential effects of radiation on key performance domains that are expected to be most critical to mission success. NASA recognizes that the academic community and research sponsors have devoted considerable efforts to vetting the translation of results from animals to humans in areas of mental health. Two examples of such efforts are the batteries of tasks for evaluating cognitive domains in animals (+/- external perturbations) in the context of schizophrenia that were devised by the MATRICS and CNTRICS panels, and the new Research Domain Criteria (RDoC) framework developed by the National Institutes of Mental Health (NIMH). NASA proposes building on these approaches to establish the best strategies to evaluate and mitigate decrements in neurocognitive performance and behavior specific to radiation exposure and the potential interaction of radiation with other spaceflight stressors of relevance to behavioral health and performance.

Spaceflight relevant doses of simulated space radiation cause decrements in behavioral performance in rodents, and induce alterations in neuronal structure and electrophysiological parameters, suggesting that analogous changes may occur in astronauts. However, the experimental approaches used for these rodent studies have been diverse, not well-standardized to allow generalization from one study to another, and may not optimally support translation to humans. To conduct a comprehensive risk assessment and manage health risks for astronauts of future exploration missions, the combined effects of radiation and other spaceflight stressors must be assessed using highly reliable models that can bridge the gap between the radiation-induced effects observed in animal models and the predictions of specific outcomes in human performance in space.

To address these needs a workshop was conducted in June 2017 to develop consensus on cognitive and behavioral test batteries and associated biomarkers that (1) support the translation of animal models to humans, (2) are conducive to testing decrements due to radiation and other

spaceflight stressors, and (3) are suitable for evaluating mission-acceptable countermeasures. Participants of the workshop developed summary tables of recommended behavioral batteries that link human and animal constructs, and provided summary reports that contain the detailed consensus of their views. These reports and tables as presented in the body of this workshop report.

Agenda of Meeting

A workshop sponsored by two of NASA's HRP Elements (Space Radiation [SR] and Human Factors and Behavioral Performance [HFBP]) was held at the South Shore Harbour Resort and Conference Center, League City, TX on June 13 and 14, 2017. The workshop, titled *Optimization of Translational Animal Models to Assess Human Spaceflight Performance for Studying the In-Flight Effects of Space Radiation: The Journey to Mars and Back*, brought together NASA funded investigators and external experts. The goals of the workshop were to evaluate current paradigms and identify the best approaches for translating animal data to human performance measures that will allow NASA to assess potential performance decrements due to radiation and other spaceflight stressors (e.g., isolation and confinement) and to evaluate acceptable countermeasures. The agenda is shown in Appendix A.

The workshop started with the following overview presentations describing evidence from behavioral, psychological, and radiation studies used to evaluate health risks to astronauts on spaceflight, behavior and cognitive domains that are important during spaceflight, and the effects of space radiation exposure:

- *Optimization of Translational Animal Models to Assess Human Spaceflight Performance for Studying the In-Flight Effects of Space Radiation: The Journey to Mars and Back* by Lisa C. Simonsen, PhD (Space Radiation Element Scientist, NASA Langley Research Center)
- *Space Radiation/Human Health and Behavioral Performance Workshop: Cognitive and Behavioral Domains* by Thomas J. Williams, PhD (HFBP Element Scientist)
- *Space Radiation and Responses of Animal CNS* by Gregory Nelson, PhD (Discipline Lead, CNS Radiation Element)

Richard Britten (Eastern Virginia Medical School) then presented the executive summary of NASA task *The Human-to-Animal Mapping Matrix for High Priority Domains*, a preliminary evaluation of current animal and human behavioral models and their status and applicability for estimating human risks from spaceflight. Next, Gregory Nelson presented the charge to the panel that summarized the goals and the objectives of the workshop.

Nine extramural space radiation investigators (R Britten, C Davis, A Eisch, C Lemere, C Limoli, B Rabin, J Raber, S Rosi, R Vlkolinsky) then delivered brief presentations that addressed the following four questions.

- What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?
- Which non-radiation spaceflight factors are amenable to animal based testing? Are there promising approaches for testing their interactions with radiation?
- Can we define a set of core measures and test conditions for animals that translate to human measures?

- What problem definition and guidance is needed from the HFBP community and external experts?

Four HFBP investigators (R Gur, G Light, P Roma, R Rose) then delivered brief presentations that addressed the following four questions.

- What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?
- Which spaceflight factors have the greatest potential to negatively impact the domains that you evaluate? Are there promising animal analogs that might enable testing their interactions with radiation?
- Based on current human data and the R Britten initial assessment, what are the main limitations to evaluation of human impairments and what is needed?
- What problem definition and guidance is needed from the animal & radiation community and external experts?

Lastly, eight external experts (M Hoefer, H Moore, V Risbrough, C Stark, L Tecott, R Turner, J Young, J Zeitzer) delivered short presentations describing their expertise and addressed the following questions:

- What principles and strategies best establish the validity of translational models and how can we apply them to NASA's special circumstances?
- What criteria can be used to determine when a spaceflight environment-elicited change has reached significance in terms of health and performance? Are there animal equivalents?
- Based on evidence reports and the R Britten initial assessment, what radiation elicited changes in animals likely impact critical neuropsychological domains in humans?
- Are there a set of core measures that could best be used to translate between animals and humans?

All presentations are provided in Appendix B.

The participants were then split into four groups for concurrent sessions to facilitate in-depth analysis of the following specific translational areas:

Session 1: Translational Models of Cognitive Performance & Circadian Dysregulation

This group focused on the relevance of successful animal models for evaluating human circadian dysregulation and performance related to cognitive processes including learning and memory.

Session 2: Translational Models of Neurobehavioral Performance

This group focused on exploring methods for increasing bidirectional translation of research findings between animal models of mood and arousal systems (e.g., depression, anxiety, asthenia, fear, avoidance, etc.).

Session 3: Translational Models of Social Systems and Processes

This group focused on the underlying neurobiological and psychological mechanisms of stress buffering in social relationships by exploring translational models of avoidance, withdrawal, and arousal that may influence a social buffering process.

Session 4: Translational Models of Neurocircuitry

> *This group focused on translational models that have demonstrated regulation of neurocircuitry, and relationships between neurobiological and psychological mechanisms. The goal was to identify translational approaches that employ integrative models of neurocircuitry and incorporate multiple levels of analysis (e.g., molecular, cellular, physiological, social processes) to address potential biological control of behavior and performance.*

The groups were asked to develop consensus on a standard test battery of cognitive and behavioral tests that

- support validated translation between animal models and humans.
- are conducive to testing impairment due to spaceflight stressors.
- are conducive to evaluating mission acceptable countermeasures.

The following materials were provided to each group to assist with capturing their recommendations.

- NASA evidence reports summarizing current knowledge in radiation and human behavioral medicine risk areas (humanresearchroadmap.nasa.gov/Evidence)
- Executive summary and human to animal mapping matrices from R. Britten/S Deutsch report (Provided in Appendix C)
- Focus questions and issues (as discussed below)

Participants

The breakout sessions and list of participants are identified below.

1. **Translational Models of Cognitive Performance & Circadian Dysregulation**

    - Richard Britten, PhD, Eastern Virginia Medical School (Moderator)
    - Alexandra Whitmire, PhD, KBR/NASA-JSC (NASA facilitator)
    - Ruben Gur, PhD, University of Pennsylvania
    - Bernard Rabin, PhD, University of Maryland
    - Jared Young, PhD, University of California ,San Diego
    - Jamie Zeitzer, PhD, Stanford Center for Sleep Sciences and Medicine
    - Kristine Ohnesorge, MSc, NASA-JSC (scribe)

2. **Translational Models of Neurobehavioral Performance**

    - Jacob Raber, PhD, Oregon Health and Science University (moderator)
    - Jason Schneiderman, PhD, KBR/NASA-JSC (NASA facilitator)
    - Charles Limoli, PhD, University of California, Irvine
    - Raphael Rose, PhD, University of California, Los Angeles
    - Lawrence Tecott, MD, PhD, University of California, San Francisco
    - Victoria Risbrough, PhD, University of California, San Diego
    - Zarana Patel, PhD, KRB/NASA-JSC (scribe)

3. **Translational Models of Social Systems and Processes**

- Amelia Eisch, PhD, University of Pennsylvania (moderator)
- Lauren Landon, PhD, KBR/NASA-JSC (NASA facilitator)
- Laura Bollweg, NASA-JSC
- Sophia Bulatova, NASA-JSC
- Catherine Davis, PhD, Johns Hopkins School of Medicine
- Matthew Hoefer, DO, Uniformed Services University of Health Sciences
- Holly Moore, PhD, Colombia University Medical Center
- Pete Roma, PhD, KBR/NASA-JSC
- Diana Arias, MSc, KBR/NASA-JSC (scribe)

4. **Translational Models of Neurocircuitry**

- Janice Huff, PhD, MEI Technologies/NASA-JSC (NASA facilitator)
- Cynthia Lemere, PhD, Harvard Medical School
- Gregory Light, PhD, University of California, San Diego
- Sarah Lumpkins, PhD, KBR/NASA-JSC (scribe)
- Ajitkumar Mulavara, PhD , KBR/NASA-JSC
- Susanna Rosi, PhD, University of California, San Francisco (moderator)
- Craig Stark, PhD, University of California, Irvine
- Rob Turner, PhD, University of Pittsburgh
- Roman Vlkolinsky, PhD, Loma Linda University

Charge to Panels

Workshop participants were asked to examine and develop a consensus on the use of standardized assessment tools for analogous rodent and human behavior and performance parameters that could be used to assess in-mission risks of potential central nervous system (CNS) decrements due to combined radiation and isolation/stress exposures. Suggested content for the workshop report were provided to the participants.

The groups were directed to

- review evidence for radiation-induced changes in animal outcome measures and assess relevance to changes in human outcome measures important for spaceflight.
- identify the most relevant and valid performance characteristics for each outcome measure and identify the key underlying biological processes and structures in animal models that translate with high confidence to human outcome measures.
- recommend best practices for translating animal measures to human measures to estimate their influence on permissible outcome limits or operationally significant degradation of performance.

The groups were also asked to provide the following deliverables when assessing validity of proposed model systems.

1. A summary of the current state of science of translational animal models for neurobehavioral and neurocognitive research that includes
    a. recommended models that are well validated and can readily be adopted for use by NASA for experimental radiobiology.
    b. models that are currently being used, but that may require modification for use in NASA studies.
    c. areas where no models are currently available or where the models may be difficult to apply to NASA domains and/or countermeasure testing.
2. Consensus table of outcome measures and models
3. Recommended models by human domain of concern
4. Examples of successful use of animal paradigms that predict cognitive or behavioral outcomes in humans
5. Answers to the following questions:
    a. Can human cognitive and behavioral effects from combined radiation and other spaceflight stressors (e.g., isolation) be evaluated in animal models?
    b. Are there potential "reference stressors" that could be used as standards for assigning levels of significance to radiation-induced changes that would guide translation of results to humans (e.g. equivalent blood alcohol levels, degree of sleep deprivation, etc.)? How would effects of reference stressor best be measured in rodents and humans?
    c. How well do animal measures and human mission-relevant outcome measures correlate?
    d. Are current animal models adequate or would research benefit from new or improved models?
    e. What are validation criteria for translatability and does the suite of identified models provide sufficient cross-validation of measured outcomes?
    f. Is the use of multiple models employing different approaches to provide converging evidence a requirement?
    g. What are the relevant translational models from the Research Domain Criteria neurocircuitry systems?
    h. How can we identify and interpret underlying perturbations in functional neurocircuitry to assess complex cognitive processes?
    i. What minimally invasive biomarker approaches (For example: biological responses, neuroimaging, performance change, etc.) would best support animal to human translation?
    j. Can the effectiveness of countermeasures, including exercise, diet, pharmaceuticals, and training, be tested and validated in the identified suite of models?

Gaps in Research Knowledge defined in the Human Research Program's roadmaphttps://humanresearchroadmap.nasa.gov/

Reports from Each of the Breakout Sessions

Session 1 Report: Translational Models of Cognitive Performance & Circadian Dysregulation

Group 1 was tasked with reviewing the relevance of successful animal models for evaluating human circadian dysregulation and performance related to cognitive processes including learning and memory.

1. ***Summary*** of current state of science of translational animal models for neuro-behavioral and neurocognitive research and recommendations for future work.

Current state

Multiple studies have reported that accelerated charged particles, as surrogates for galactic cosmic ray (GCR), impair several cognitive domains in rodents.

- In some domains, the results of multiple assays agree.
- Some inconsistencies exist, which may result from differential environmental factors and associated epigenetic mechanisms and from interactions between genetics and environment.
- Overall, there is a good coherence of animal tests in use with the human "COGNITION" battery in use with astronauts (a few additions and a few improvements)
- Multiple species have been examined.
- Multiple strains of rodents have been examined.

Recommendations for future work

- A standard rodent 5-Test battery (4 cognitive domains, 1 psychosocial) should be developed because individual variance in multiple domains translate to psychiatric disorders in humans (e.g., schizophrenia drug trials). Also, most neurological disorders are characterized by changes in performance in multiple cognitive domains; thus a composite score of drug-induced changes in a battery of tests is commonly used to evaluate new therapeutic agents (e.g., MATRICS Consensus Cognition Battery, MCCB for schizophrenia (Kern et al, 2008). A similar approach is probably needed to determine if mission-relevant GCR doses could impair performance in the three or four cognitive domains that NASA considers to be most critical for mission success, and to build a probabilistic acute risk assessment using the composite data from such studies. Therefore, the panel agreed that a move to a multi-parameter assessment is required in rodent studies.
- Studies might require consortiums (similar to NASA's Specialized Center of Research (NSCOR) model, but with different funding and logistical profile) including central coordinators, with modest (e.g. ≈ 10%) overlap of the study design between other participants. Reproducibility is critical and could be demonstrated with this process [Editor's Note: This is not standard practice for a NASA NSCOR setup. The CNS/BMed/Sensory motor (CBS) integrated research plan includes a yearly review of progress made by individual projects and to track early failure of hypotheses pursued to exercise alternative paths forward, and is reviewed across disciplines].
- When the study population is genetically diverse, animals should be preselected to reflect the high performing astronaut population: Top ≈ 35% performers in 2 or 3 domains. Pre-

screening selects for both ability and for motivation to perform the tasks, consistent with astronaut screening. This would not necessarily be relevant if a genetic strain of animals is selected that are known to show superb cognitive performance in pertinent domains of interest and relevance for space missions.

- Individualized measurements with Z-scores or non-parametric equivalent should be assessed as independent outcome measures. Within-subjects designs are very powerful, enabling the use of smaller sample sizes. The overall test battery score would be the main metric for translation.
- Repeated measures that avoid practice effects are needed, i.e. longitudinal designs with short tests that ideally are semi-automated.
- Studies need to become more mechanistic, and more psychometric components are needed.
- Studies need to have an increased emphasis on probabilistic learning.
- There needs to be concurrent and iterative feedback with the cognition battery in HFBP spaceflight analog studies to progress towards permissible outcome limits (POLs).
- There should be cross-species validation of outcome measures (avoid individual parameter comparisons).

1a. Recommended models that are well validated and can readily be adopted for use by NASA for experimental radiobiology

Conducting multiple tasks on a single animal (as would occur in humans) would increase the breadth and value of outcome measures from charged particle irradiations, and would provide greater consistency with human testing (multiple domains) that interprets findings based on multiple domain testing. (See table1 below).

1b. Areas where models are currently being used, but may require modification for use in NASA studies

The panel thought current rodent models are reasonable: mice and rats are widely used and both have merit. It is important to recognize that in the wild rodents are very different species but all animals that have been used in radiation studies are domesticated.

The panel suggested the following refinements (for both species) for future studies.

- Animals should be physically fit when practical. [Editor's note: Animals need to be prescreened to set criteria for inclusion in study as discussed above].
- To the degree possible, animals should be tested during the active (wake) phase to conform to their natural behavior. However, this can be complicated. For example, if light is required as part of the test, that might affect circadian activity levels or make it impossible to use the test. Moreover, during a mission, astronauts are expected to perform during both active and inactive phases.
- Outbred strains are best for sampling population variability (consistency with humans).
- Animals should be pre-selected: Top 35% in 2-3 domains measured using individual metrics. The pre-screening strategy should assess some kind of motivation to do the task. This would better simulate astronauts who are highly trained. Individualized measurements

are required. Within-subjects designs are much more powerful allowing for smaller sample sizes.

The panel recommended that the following potential covariates be studied.

Social stress: Studies of the effects of isolation, confinement and environment (ICE), and habitat density should include rodents that have been subjected to social stress (increased housing density or social isolation), perhaps implemented as directed add-on studies to existing peer-reviewed competitive grants (if principal investigator [PI] can, and is, willing to do such studies).

Sex covariance. For domains where charged particle-induced (1-5 cGy) cognitive impairments are observed in males, "discovery experiments" should be conducted in males and females with, for example, 1 ion at 2 doses. From the investigator's perspective, such studies would be hard to do through a competitive grant but directed add-on grants might be appropriate. [Editor's note: All current NASA Research Announcements (NRAs) require the testing of both males and females.] A systematic study of the impact of variations in estrogen levels at the time of irradiation on radiation-induced cognitive impairment is desirable. The pertinent rodent model for female astronauts should also be determined—perimenopausal, birth control usage? The panel did not recommend using ovarectomization with estradiol supplement. [Editor's note: recent unpublished studies have found increased resistance to radiation effects in females for several CNS outcome measures (Krukowski et al. 2018).

1c. Areas where no models are currently available or where the models may be difficult to apply to NASA domains and/or countermeasure testing

Microgravity: For animal models, ground-based altered gravity level analogs (especially microgravity) are currently inadequate for behavioral assessments because hind limb unloading paradigms have stress components that must be considered (restraint stress). [Editor's note: restraint stress relates to learned helplessness models whereby contingencies of reinforcement no longer matter. Microgravity may induce a similar restraint "stressor", because astronauts are confined to a small space. Also, ground-based experiments indicate that full load-bearing cohorts can be similarly constrained to allow comparison of the "hind limb" unloading effects]. These have utility for musculoskeletal studies but it is not clear how relevant they are for cognitive and behavioral studies unless sensorimotor tasks (in particular, neurovestibular effects) are considered. The group suggested that SR and HFBP elements collaborate with NASA's Space Biology group to perform rodent studies on the impact of microgravity covariance.

Sleep: Rodent experiments are worthwhile but may not be conclusive from a sleep perspective. All sleep deprivation in animals has a significant stress component that may compound GCR-induced impairments. Sleep deprivation in humans is voluntary, or semi-voluntary, and has less of a stress component. [Editor's note: for most crewmembers, sleep deprivation experiences is not voluntary but due to insomnia, an inability to sleep even though they want to do so.] However, some findings in people that volunteer for sleep deprivation are consistent with animals that are sleep deprived—e.g., decrements in 5 choice continuous performance test (5C-CPT) performance (van Enkhuizen et al, 2014; Aylward et al, 2002).

2. *Consensus table of suggested outcome measures and models*

Table 1. *Group 1 recommendations for outcome measures and models to assess circadian dysregulation and performance related to cognitive processes including learning and memory.*

Human Construct	***Recommended Rodent Model***	***Rodent Model Deficiencies***
Fitness for duty standard (Basner et al. 2011)	Rodent 5-Test (4 cognitive domains, 1 psychosocial)	Needs to be developed. Would require a consortium. *Vide infra, supra*
Vigilant attention *Psychomotor vigilance (PVT)*	rPVT 5 choice continuous performance test (5C-CPT)	
Working memory *Fractal 2-back*	Odor Span Test Delayed (non) matched to sample test.	
Risk decision-making *Balloon analog risk (BART)*	Barrus & Winstanley, 2016, Assay Rodent Iowa Gambling Task	
Spatial learning and memory *Visual object learning (VOLT)*	Touchscreen cognitive testing (Bussey et al, 2008).	Morris Water Maze & Barnes Maze not necessarily correlated to Visual Object Learning Test (VOLT)
Perceptual executive functions	Operant set-shifting	
Abstraction, concept formation *Abstract matching*	Rodent ASST, intra and extradimensional shifts	
Metacognition Unconstrained Cognitive Flexibility	A. Kepecs' models (Kepec et al, 2018) UCFlex (Hecht et al, 2014)	

3. *Recommended models by human domain of concern.*

See table1. It likely matters when a subject is irradiated (DNA-repair mechanisms likely have a circadian component); however, little work has been done to assess interactions between the effects of radiation and dysregulation of circadian rhythms and sleep architecture. The stress induced by a slam shift before an extravehicular activity may create vulnerability through a change in circadian phase and a reduction in circadian amplitude, which may further worsen DNA-repair mechanisms. [Editor's note: effects will not be restricted to DNA repair mechanisms, but other CNS mechanisms may be affected as well].

4. *Examples of successful use of animal paradigms that predict cognitive or behavioral outcomes in humans*

The group cited the following successful models in which qualitatively similar outcomes can be quantified in animals and in humans.

- Abstraction, concept formation in animals predicts abstract matching in humans
- Wisconsin Card Sorting in humans—an analog of rodent attentional set shifting (Fox et al, 2003) that employs repeated intra dimensional and extradimensional shifts
- 5C-CPT—attention and response inhibition
- Probabilistic Learning paradigms (e.g. Averbeck et al. 2011)
- Progressive Ratio Breakpoint (e.g. Sharma et al 2012; Chelonis et al, 2011)
- Metacognition (Kepecs et al. 2008)—well validated
- Oddball paradigms (or mismatched negativity) can be used in both rodents and humans to determine how radiation exposure affects the speed of neural processing, as determined through examination of event-related potentials in electroencephalography (EEG).
- Novel Image and Novel Location can be used in humans and object recognition test containing novel locations and novel objects can be used in animals. The effects of apolipoprotein E4, a risk factor for age-related cognitive decline and Alzheimer's disease, have been demonstrated in E4-carrying humans.
- Memory Island and other (virtual reality) software programs that assess spatial learning and memory can be used in humans, and spatial learning and memory requiring navigation can be used in animals. Memory Island has been used in patients with autism-spectrum disorder, in age-related cognitive decline, and other conditions.
- Fear learning and memory have been assessed in humans and animals, e.g. in the context of post-traumatic stress disorder in humans and animal models. The severity of symptoms of posttraumatic stress disorder were assessed in apolipoprotein E2 carrying human veterans, and were compared to phenotype seen in apolipoprotein E2 carrying mice.
- The above examples focus on cognitive outcomes but forced-swim test in animals to predict behavioral performance and depression in humans would be just one of many examples for predictive behavioral outcomes.

5a. Can effects of human spaceflight stressors on cognitive and behavioral outcome measures be tested in animal models such that combined effects of radiation and other stressors be evaluated?

The group agreed this could be done; however, they debated whether the models of stress in rodents are comparable to stress in humans.

5b. Are there potential "reference stressors" that could be used as standards for assigning levels of significance to radiation-induced changes that would guide translation of results to humans (e.g. equivalent blood alcohol levels, degree of sleep deprivation, etc.)? How would effects of reference stressor best be measured in rodents and humans?

In general, the panel recognized that valid and reliable reference stressors for studying CNS effects of spaceflight-like impairment in translation models are needed.

They believed traumatic brain injury (TBI) would be valid (although still variable) as a reference stressor. Two animal models of TBI are typically used—cortical impact and fluid percussion. Cortical impact model is focused and not diffuse. Closed head injury might be more pertinent but typically has a large variability in its effects. Chronic traumatic encephalopathy, which unlike TBI does not involve loss of consciousness, may be more relevant for comparison with human spaceflight. The military probably have a fitness-to-return-to-duty standard that could be scaled to a degree of impairment in the 5-test rodent battery test.

5c. How well do animal model and human mission-relevant outcome measures correlate?

A high degree of concurrence exists between human behavioral measures and current rodent tests, and other rodent assays may be in agreement also.

5d. Are current animal models adequate or would research benefit from new or improved models?

The group suggested these new or improved models.

- Probabilistic learning, which is easy to do in humans and is being used across species (Averbeck et al. 2011)
- Abstraction/Concept Formation: Metacognition (Kepecs et al. 2008); Creative Problem Solving (Hecht et al. 2014)
- Reward Effort-Benefit (Kepecs et al. 2008); effort tasks exist in rodents and humans.
- Risk decision-making: BART in humans and rodent gambling test (Barrus & Winstanley, 2016) (BART can also be performed on rodents and Iowa gambling tasks on humans).

This breakout group concluded that there are no suitable models for emotion identification. [Editors note: other participants expressed a dissenting view and pointed out that facial recognition is being used in humans and that emotions can be assessed in animals as well.]

5e. What are validation criteria for translatability and does the suite of identified models provide sufficient cross validation of measured outcomes?

Validation criterion depend on the behavioral paradigm, e.g., for both mice and humans, parietal lobe activity affects 5C-CPT, sleep deprivation impairs 5C-CPT, and amphetamine improves 5C-CPT. Kepecs' "Metacognition" studies (Kepecs et al, 2008) have been validated in multiple rodent species, NHP, and humans.

The "COGNITION" battery developed for spaceflight (Basner et al., 2015) includes all major domains evaluated by the schizophrenia battery (MCCB), and it should be sensitive to deficits in executive function, memory, complex cognition, and social cognition. NASA has already demonstrated this cognition battery is sensitive to sleep deprivation and space analog conditions (e.g., over-wintering in Antarctica).

5f. Is the use of multiple models employing different approaches to provide converging evidence a requirement?

Regarding evidence from multiple species, spaceflight stressor investigations have already been conducted in mice and rats. Studies with NHPs are potentially useful, but the increased applicability to humans may be offset by the increased impact of environment and social interactions on NHP behavior. However, NHPs offer the possibility of using a broader array of cognitive tests, and if they show the same pattern, this can be regarded as converging evidence.

5g. What are the relevant translational models from the Research Domain Criteria neurocircuitry systems?

The primary focus to date has been on hippocampus-dependent tasks. NASA needs to explore more tasks that depend on other brain regions, especially frontal cortex -related tasks wherein decision-making occurs. A potential standardized rodent battery would cover most RDoC Constructs except for approach and avoidance, facial expressions, freezing, open field, and response inhibition. Negative Valence Systems can be assessed by measuring punishment sensitivity in the probabilistic learning and Iowa gambling tasks.

Brain-wide circuitry in animals should be assessed and reassessed with tests that can be translated to humans. Task-probes rather than testing-probes would measure neurocircuitry more widely and tap into bigger and broader networks that can evaluate parameters on a larger scale.

Mismatch negativity or "oddball" paradigms may be useful models.

NASA needs to determine which region(s) of the brain are most likely to be affected during the mission due to spaceflight stressors because there may be regional vulnerability and anatomical specificity.

5h. How can we identify and interpret underlying perturbations in functional neurocircuitry to assess complex cognitive processes?

The group recommended the following methods.

- Consider using optogenetic techniques to mimic and/or rescue deficits
- Conduct more circuit-based investigations rather than looking at specific tasks
- Quantify neuro-inflammatory markers that can parallel changes
- Conduct unbiased pathway analyses using omics approaches

5i. What minimally invasive biomarker approaches (fluid-based, neuroimaging, etc.) would best support animal to human translation?

The group advocated using neuro-inflammatory markers and neuroimaging that can parallel observed behavioral changes. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are useful for assessing neuroinflammation and resting state connectivity, and can be performed on rodents. However, both these imaging methods are problematic for assessing real-time changes during task performance because these procedures are best performed on anesthetized rodents. Performing these procedures on awake (constrained) subjects places an enormous amount of stress on the rodent. Measuring local field potentials during task performance would be more informative and would provide information on neural

circuitry that is affected by radiation. The group suggested establishing collaboration with the National Institutes of Health who are funding several cognitive testing/EEG studies.

Efforts to develop plasma biomarkers for neurodegenerative conditions and cancer are ongoing; one potential candidate could be microRNA levels. Biomarkers based on the gut microbiome could be developed; in some studies, human material was used to induce disease in mice, showing the translatability of this approach.

5j. Can the effectiveness of countermeasures, including exercise, diet, pharmaceuticals, and training, be tested and validated in the identified suite of models?

The group believed that diet could be a better countermeasure than pharmacological approaches.

They also suggested

- investigating cognitive training with simple stimuli to improve sensory processing that could lead to sustained improvements in working memory. If a battery of tasks demonstrated deficits in specific domains, then targeted training could be established.
- developing enhanced drug delivery and stabilization methods appropriate to spaceflight.
- determining whether existing neurotrophic drugs would be beneficial as countermeasures.
- identifying circuitry underlying impaired performance during pharmacological interventions.

Session 2 Report: Translational Models of Neurobehavioral Performance

Group 2 was tasked with reviewing methods for increasing bidirectional translation of research findings between animal models of mood and arousal systems (e.g., depression, anxiety, asthenia, fear, avoidance, etc.)

1. Summary of current state of science of translational animal models for neuro-behavioral and neurocognitive research and recommendations for future work

Well-validated neurobehavioral animal models exist that can predict drug responses in human populations. From a practical point of view, and based on the current gaps in knowledge, the group concluded that rodents are the best option for addressing effects of radiation that can be extrapolated to humans, and can provide an understanding of the underlying caveats. The group also concluded that it would not be feasible to try to address the gaps using higher species, except perhaps for a relatively small and less involved study that addresses well-defined questions.

The group also noted that NASA's human standard measures for the behavioral/affective area are less well developed than those for the cognitive, sleep/circadian, and social areas, and if they are improved this would benefit the work in addressing the effects of radiation and translation of data to rodents and other animals.

The group discussed the ability to assess the effects of combined environmental stressors using the available models, and they recommended using environmental stressors combined with sleep deprivation because fatigue is highly stressful for astronauts.

The group suggested manipulating cage size to model the effects of the confined space. The group discussed altered carbon dioxide levels, however, based on the data from previous experiments, they concluded that mission-relevant CO_2 levels would have little, if any, impact on behavioral or cognitive performance (Ryder et al. 2017; Stankovic et al. 2016).

The criterion for candidate animal models and test paradigms listed below might guide the selection of validated test paradigms that NASA could adopt to determine effects of space irradiation on behavioral outcome measures.

- Radiation responsive
- Ability for repeated use/testing
- Ability of rats and/or mice to perform the test
- Ability for unbiased and/or automated observations and analyses
- No extreme resources required

2. Consensus table of outcome measures and models

The group provided the following list of candidate experimental measures and paradigms that are currently being used and could be considered for use in NASA-supported studies. The <u>underlined</u> text identifies measures and paradigms that can address question 5c because animal measures and human mission-relevant outcome measures correlate.

Candidate experimental measures and paradigms[1]

- Immobilization stress; plasma corticosterone levels (HPA) as a measure of the stress response; however, this may not be responsive to low doses of radiation
- Light-dark box without elevation as a measure of anxiety/avoidance
- Acquisition and extinction of learned fear measured by freezing, operant or startle behaviors as a measure of learned fear, fear inhibition, fear generalization
- Explorative behavior and measures of anxiety in open areas (open field, light-dark box) and elevated anxiety provoking areas (elevated zero maze; elevated plus maze) as a measure of anxiety, curiosity drive, and mood[2]
- Sucrose preference test, intracranial self-stimulation [reward processing, anhedonia] (not based on ambulation) to address depression-like behavior and reward system disruption
- Forced swim and tail suspension tests as a measure of depression
- Pathway changes in the CNS that could be associated with changes in markers in peripheral tissues or body fluids
- Cage size modification[3] as a measure of chronic stress to model relative small space environment during space missions

[1] The underlined text indicates measures and paradigms that are able to address question 5c (for details, see text).
[2] Use of light-dark box was also suggested.
[3] Cage size stress might also take the form of overcrowding as rodents prefer small spaces.

Other paradigms discussed but not recommended included stress-induced hypothermia and heart rate variability.

3. *Recommended models by human domain of concern.*

Table 2b includes proposed animal models for predicting changes in human behavior or cognition. Models that can be used for cross-species comparative studies and that are predictive are most desirable. Alternatively, models that are known to induce/trigger similar clinical outcomes across species would be useful as they presumably involve similar pathophysiology. Both types of models can be used to validate predictions, which will be critical. Animal models can include genetic models, pharmacological models, and environmental models or a combination of them in a single model.

Table 2b. *Animal models that may predict changes in human behavior or cognition.*

Animal Model/Paradigm	***Human Counterpart***	***Reference***
Cage size modification	HERA	Hughes et al. 1989
Home cage monitoring Unbiased continuous video monitoring to generate quantifiable behavioral measures for translational use in human	Smart homes	Johnson et al. 2015; Birchley et al. 2017; Demiris & Hensel 2008

4. *Examples of successful use of animal paradigms to predict cognitive or behavioral outcomes in humans*

Table 2c. *Examples of animal paradigms that have been successfully used to predict changes in human behavior or cognition.*

Test	***Prediction of Behavioral Outcome in Humans***	***Reference***
Elevated plus maze and elevated zero maze	Anxiolytic effects; for example from benzodiazepines	Helton et al. 1998; Kralic et al. 2002; Kulkarni et al. 2007; Linden et al. 2004.
Forced swim test	Anti-depressive effects; for example of SSRIs and ketamine	Mason et al. 2009; Perona et al. 2008; Yoshikawa et al. 2002.
Spatial navigation		Berteau-Pavy et al. 2007; Moffat et al. 2002.
Fear conditioning and extinction	D-cycloserine	Milad et al. 2011; Matsuoka & Aigner 1996; Bolkan & Lattal 2014; Glenn et al. 2014.
Hippocampal based memory paradigms	Post-trauma or prior memory testing administration of glucose to activate hippocampus and contextual learning.	Glenn et al. 2014; Johnson et al. 2017
Object recognition	Age-related cognitive decline; mild cognitive decline (MCI); neurodegenerative conditions and dementias.	Berteau-Pavy et al. 2007; Haley et al. 2010; Haley et al. 2012; Rizk-Jackson et al. 2006; Raber et al, 2015.
Sleep deprivation manipulation in conjunction with performance test(s)	Sleep deprivation/fragmentation tests in humans	Toth & Bhargava 2013

5a. Can effects of human spaceflight stressors on cognitive and behavioral outcome measures be tested in animal models such that combined effects of radiation and secondary stressors be evaluated?

The group believed this can be done, and that it is actually already taking place. Secondary stressors could include sleep deprivation, overcrowding, cage modification, and physical or emotional stress. In addition, the group suggested that NASA consider genetic factors because genetics can increase susceptibility of developing detrimental effects from space radiation. Indeed, other than passive measures such as assessment of home cage activity or physiological functions (e.g. via telemetry), most tests of humans and animals induce some level of stress themselves; at a minimum, the stress associated with exposure to novelty.

5b. Are there potential "reference stressors" that could be used as standards for assigning levels of significance to radiation-induced changes that would guide translation of results to humans (e.g. equivalent blood alcohol levels, degree of sleep deprivation, etc.)? How would effects of reference stressor best be measured in rodents and humans?

The group discussed blood alcohol concentration (BAC) as a reference stressor to establish an acceptable risk to the CNS from radiation. For example, less than 6 hours of night sleep could equate to a specific BAC with regard to reaction time and ability to operate a vehicle/navigate. The group thought that reference stressors might be more appropriate for assessing cognitive

function than behavioral performance (e.g., anxiety and depression). However, after considering the inverted U-shape relationship between stress and cognitive performance, the group determined that would be challenging to develop threshold limits for behavioral outcome measures; for example levels of pathological anxiety or depressive behaviors. The panel suggested that translatability could be increased by leveraging data on how stress affects cognitive constructs. Ultimately, the effects of stress on cognitive performance may be more important than increased anxiety or depression. A strategy here would be determining what the threshold of impairments are in humans and consider using these as operationally significant criteria. The group recognized the challenge of developing these operational criteria because of inter-individual human responses. If the crewmembers are willing to share the details of their private psychological conference with the flight surgeon, this could assist in the effort for defining operational significance based on crew concerns. The group agreed that it is important to derive a pattern or signature by collecting as much data as possible from individual humans and animals, rather than relying on a single behavioral assay or outcome measure. It may be helpful to consider brain performance pathways that change as a function of space radiation exposure. The breakout group wondered if the scientific literature includes any quantified level of change that is currently being used as a trigger point/threshold.

Since serotonin levels in humans can be manipulated to induce depression, the group thought it would be feasible to map decrements in behavioral performance in animals based on the behavioral decrements in humans, although this method has not been extensively used or tested.

The group concluded that reference stressors are in principle feasible but it might be challenging to develop and validate reference standards. Stressors themselves are difficult to standardize across species. Even something that can be presented to both species, such as foot shock, is likely much more stressful to a rodent because the rodent, unlike humans, cannot anticipate or consent to the stressor. Use of homologous measures of the effects of stress across species could support such a standardization effort without relying on "face validity" of the stressor itself.

5c. How well do animal model and human mission-relevant outcome measures correlate?

Correlation depends on the specific outcome measures. The group provided the following examples of behavioral outcome measures that correlate well between humans and animals and are mission-relevant.

- Startle response
- Behavioral extinction
- Plasma levels of stress hormone (cortisol or corticosterone)
- Markers of inflammation and neuroinflammation
- Heart rate variability (which is related to emotional arousal)
- Sucrose preference
- Impulsivity
- Measures of social interaction
- Novelty detection
- Exploratory behavior in novel environments
- Spatial navigation
- Fear learning
- Memory

The group recognized though, that for some animal models, the relationship with human mission-relevant outcome measures is less clear.

Comparing composite scores for each animal with the same types of scores in humans is valuable; this approach is being used for analysis of home cage activity in mice. The group reiterated that integrating individual outcome measures for as many domains as possible would be preferable to relying on a single outcome measure or test. Z-scores could be used to generate composite behavioral and/or cognitive scores. Relationships between various outcome measures in distinct tests can be identified using principal component analyses, and subsequent analyses could be performed using the identified components that account for of the most variance. Identifying alterations in behavioral performance pathways in animals would be valuable in guiding which performance pathways to characterize in humans. For example, when there is a significant effect on extinction in animal behaviors, the animals might be more likely to exhibit measures of anxiety and depressive-like behaviors. In addition, the neurocircuitry involved in fear learning and memory is well known, and therefore the data generated from the animal studies can be used to guide fear learning and memory studies in humans. Definable sub-constructs in the animal models might be helpful in such efforts as well.

5d. Are current animal models adequate or would research benefit from new or improved models?

Current animal models are adequate for addressing the CNS-related knowledge gaps and risks.

5e. What are validation criteria for translatability and does the suite of identified models provide sufficient cross validation of measured outcomes?

As the group has reiterated throughout the review, the use of homologous measures is critical for validation. The discussion of reference stressors in section b is relevant also.

5f. Is the use of multiple models employing different approaches to provide converging evidence a requirement?

The group did not agree whether this should be a requirement. They were also not clear whether the requirement refers to guidelines for research funding or astronaut protocols. However, the use of single outcome measures or assays should be discouraged. As indicated earlier, having multiple outcome measures or assays for modeling the psychological process(es) of interest is more scientifically rigorous and thus preferred.

5i. What minimally invasive biomarker approaches (fluid-based, neuroimaging, etc.) would best support animal to human translation?

The group suggested EEG, cardiovascular-related measures in the CNS, and approaches for analyzing biomarkers of inflammation, biomarkers of the gut microbiome, and for monitoring circadian activity levels. The group also agreed that neuroimaging and ultrasound are also valuable approaches; however, they are expensive and have lower spatial resolution in rodents than in humans.

5j. Can the effectiveness of countermeasures, including exercise, diet, pharmaceuticals, and training, be tested and validated in the identified suite of models?

Yes, the effectiveness of countermeasures can be tested and validated in the models.

The group discussed the need for scaling behavioral measures in animals to behavioral measures in humans, and how this could be accomplished. They questioned at what point an effect in animals is clinically or operationally relevant in humans (i.e. is important to NASA), either before, during, or after the mission(s). [Editor's note: operationally relevant performance decrements capable of impairing mission operations may not be as severe as a clinical threshold.]

The group discussed a strategy of identifying the significant performance problems that are most likely to occur in humans using severity scores, deconstruct the performance into component behaviors, then look at analogous behavioral performance of animals to enable extrapolation from animals to humans. The group also suggested tracking real time changes in astronaut behavior and focusing on using more objective, quantifiable approaches to assess changes in anxiety and mood. Behavioral patterns that emerge during spaceflight (or analogs of spaceflight) could then be gauged by passive monitoring techniques such as physiological (e.g. wearables) and/or behavioral assessments via tracking technology and these data could then be compared with clinical effects. Salivary measures of hormone, enzyme, and cytokine changes are being used to gauge mood and anxiety. The group recommended implementing research that will allow NASA to identify the relevant human domains/subdomains to determine pertinent risks to the brain during and after spaceflight missions. This research could guide subsequent mechanistic studies in animals that can interrogate critical circuitry and pathways, and can extrapolate results across species. These structured efforts will ultimately aid in the rationale development of targeted countermeasures for improving neurocognitive function and reducing early and late CNS risk associated with deep space travel.

Session 3 Report: Translational Models of Social Systems and Processes

Group 3 was tasked with reviewing the underlying neurobiological and psychological mechanisms of stress-buffering in social relationships by exploring translational models of avoidance, withdrawal, and arousal that may influence a social buffering process.

1. ***Summary: Current state of science of translational animal models for neurobehavioral and neurocognitive research***

The group discussed human constructs that can currently be assessed via preclinical models, and the existing preclinical paradigms and experimental designs. The group then identified human neural substrates that are homologous in animals and can be used to predict behavioral outcomes associated with social cohesion. In this manner, the group identified 8 animal models with high multidimensional weighting, 2 with medium multidimensional weighting, and 12 with low multidimensional weighting.

Processes for assessing social cohesion that include parameters for reproducibility and that have currently available information on translation from animals to humans were prioritized using the following categories of multidimensional weighting.

- High—Process is important for astronauts and mission success, can be tested with current animal models
- Medium—Process is important for astronauts and mission success, can be tested with current animal models after significant modifications
- Low—Process is less important or has unknown relevance for astronauts and mission success, is not currently testable in laboratory animals
- Operations Analog—predicted to have significant impact on a "Team" measure.

1a. Recommended models of social systems and processes that are well validated and can readily be adopted for use by NASA for experimental radiobiology

Models with high multidimensional weighting, as shown in Table 3, include those that address the human constructs of social reinforcement (place conditioning, operant conditioning), social drive and motivation (social approach), defensive behaviors (single incident resident intruder, repeated psychosocial defeat stress), social discrimination (acquisition and retention of olfactory social discrimination), and social hierarchy (tube dominance test).

1b. areas where models of social systems and processes are currently being used, but may require modification for use in NASA studies

Models with medium multidimensional weighting, as shown in Table 3 include those that address the human constructs of communication (affective vocalization) and sexual behavior (competition for mate).

1c. areas where no models of social systems and processes are currently available or where the models may be difficult to apply to NASA domains and/or countermeasure testing

Models with low multidimensional weighting, as shown in Table 3, include those that address the human constructs of sexual behavior (mating behavior), conspecific social conflict (ambiguous social situation), emotional attachment (pair bonding), altruism (maternal or paternal behavior), empathy (lever press to have access to a cage mate or to rescue a cage mate from aversive situation), communication (social transmission of food preference or cookie jar, bystander pain assessment), and cooperation/coordination (chain pulling, play behavior).

2. Consensus table of outcome measures and models

Table 3. *Group 3 recommendations for outcome measures and models to assess social cohesion.*

Human Construct	Animal Construct	Paradigm/Tools (beh. task)	Independent Variables	Outcome Measure	Operational Analog	Radiation Sensitive?	Other flight stressor sensitive	Amenable to counter measure efficacy (in lab animal)	Translational neural systems (region, neurochemicals, radiological target, etc.)	Notes (explains priority)
High Priority										
Social Reinforcement	Social Reinforcement	Place Conditioning	Familiarity (conspecific cagemate), sex, estrus female, offspring	Latency to approach; time spent; extinction; reinstatement	Proximity; shared social activities; content analysis	Unknown for HZE Y for X-ray	Y	Y	Striatal (mostly ventral), lateral hypothalamus, if estrud then medial preoptic, amygdala. Dentate gyrus neurogenesis is involved, sensitive to X-ray	At least 3 choices for adequate controls. Can add motivational components (ramps, runways). Extinction is not unlearning, but rather new learning. Can be conditioned to prefer or avoid.
Social Reinforcement	Social Reinforcement	Operant Conditioning	Familiarity (conspecific cagemate), sex, estrus female, offspring	Breakpoint, response rate, demand intensity, demand elasticity	Proximity; shared social activities; content analysis	Y	Y	Y	Striatal (dorsal and ventral), lateral hypothalamus, if estrus than medial preoptic	Willing to work for access to social reinforcer. Behavioral economics (see Rabin, Davis, Eisch, Britten, others)
Social Drive or Motivation	Social Drive	Social approach	Familiarity (conspecific cagemate), sex, estrus female, offspring	Latency to approach; time spent	Proximity; shared social activities; content analysis	Unknown	Perhaps stress work?	Y	Main and accessory olfactory pathways (hypothalamus, medial amygdala), prefrontal cortex (particularly ventromedial), lateral hypothalamus, bed nucleus of striaterminal, infralimbic, terla tecta	Can be test-retested with new social target/stimuli. Time countermeasure administered is important (chronic, acute) . Rats don't have prefrontal cortex granule cells, not sure it is a problem
Defensive Behaviors	Social Avoidance/Aggressi on	Resident Intruder	Familiarity (conspecific cagemate), strain, sex, estrus cycle, length/complexity of residence, complexity	Latency to approach; time spent; latency to attack; number of attacks, severity of attack	Response to conflict	Unknown, maybe for X-ray	Y	Perhaps not	Main and accessory olfactory pathways (hypothalamus, medial amygdala), lateral hypothalamus, lateral habenula, septum bed nucleus of stria terminal, PFC perhaps inhibiting behavior	Separate measures for resident vs intruder. Questionable countermeasures testing since not as amenable to oaometericze. More binary than multilevel independent measures. Categorical intruders, perhaps
Defensive Behaviors	Social Avoidance/Aggressi on	Psychological Defeat stress	strain, sex, age, estrus cycle, length of residence, complexity of residence, sensory contact during adjacent living, number of defeat bouts	Latency to approach; time spent; latency to attack; number of attacks, severity of attack, social interaction response (approach/avid)	Response to conflict	Unknown for HZE, Y for X-ray	Y	Y	Lateral hypothalamus, lateral habenula, hippocampus, septum, PAG, PFC perhaps inhibiting behavior. Lesion of OB? Dentate gyrus neurogenesis (SVZ?). Sensitive to SSI (benzo?).	separate measures for resident vs intruder
Social Discrimination	Social Discrimination: affiliative v's antagnistic	Olfactory Social Discrimination	Target (social vs. nonsocial): exploration time	Latency, duration, proportion of sniffing: habituation over time; dishabituation; discrimination index	social cohesion	HZE in progress, Y of X-ray	Y	Y	Perirhinal, olfactory and possible rostral migratory stream neurogenesis (in olfactory discrimination), conflicting results in humans.	Animal construct is not an ideal fit to human construct. Only a social cue is needed (e.g. dirty bedding) limiting relevance of "emotional recognition". However, is a good way to measure fundamental part of the constellation of social system, and social discrimination. At least 3 choices. Sensitive to (restraint?) stress. Timing of countermeasure administration is critical. Fundamental to discriminate familiar vs novel for other tests. Consider nonvolatile and volatile cues.
Social Discrimination	social Recognition: memory	Olfactory Social Recognition with retention interval	Familiarity (conspecific, cagemate), Target (social vs. nonsocial)	Latency, duration, proportion of sniffing: habituation over time; dishabituation; discrimination index						
Social Hierarchy	Social Dominance	Tube test (tube of war)	Length of pairing, strain, genetics, life experience, coping biases; whisker trimming with cage mates-indicator of dominant animal in cage (animal that trims whiskers of other animal wins in tube test)	Win probability, latency to win?	Conflict, Group Living	unknown	Unknown (genetics and housing condition likely, perhaps circadian)	Y	PFC	Translational relevance in assessing territorial, resource-guarding, hoarding. Easily modifiable, translational (rodent→NHP→primate). Used as model for autism. Latency to win not often used but could be useful. Strategy not examined but could be. Test-rest feasible. Convergent validity.
Medium Priority										
Communication	Social transmission of state	Affective Vocalization	Separation from something bonded to, solicitation behavior for sex	Hertz and rate of ultrasonic vocalization	High risk communication, task completion, voice intensity					Circuity of vocalization in lab animals is ell examined and manipulated. Neural underpinnings are reasonably well probed. However, most work is in young animals decreasing priority for translational relevance. Good discussion on utility of modulation of voice intensity/complexity as potential biomarker in missions. Possibly secondary/exploratory aim as part of another study. Best model is non-human primate (NHP)
Sexual Behavior	Sexual Behavior	Competition for mate			Competition for close affiliation					Interfering behavior
Low priority										
Sexual Behavior	Sexual Behavior	Mating behavior	Familiarity (conspecific, cagemate), strain, sex, age, estrus cycle, ovariectomy female, castrated males							Receptivity
Conspecific Social Conflict	Conflict Induced Aggression	Ambiguous social situation	Familiarity (conspecific ,cagemate)	Latency to attack, freeze, or flee. Duration of attack or freeze						Ambiguous social situation
Emotional Attachment	Attachment	Pair Bonding	Strain, sex, ae	Probability of bonding, separation behaviors	Questionnaire, crew cohesion					Pre-mission relationships; can get at same systems with social motivation assays. Better rodent models needed
Altruism	Parental Behavior	Maternal/Paternal behavior	Age, parity	Number of licks, nesting spread, active vs passive	Group Living: Sharing Food					High priority for mission but lack mission-relevant and altruism-validate rodent models. Timeframe too short, and have other models to examine related constructs.
	Allo-parenting				Group Living: Sharing Food					
Empathy	Referred to in literature as Empathy	Release cagemate vs reward ("save your rat friend from drowning")	Assess reinforcing properties of the non-social alternative	Latency to release, probability of release	Group living, social support, cohesion					Lack rodent models. Important to consider for mission and for housing of animals but not validated for empathy
	Referred to in literature as Empathy	lever pressing to have access to cagemate								
Communication	Social transmission of information	Social transmission of food preference	length of pairing, strain, genetics, life experience, cooping blases	latency to eat food , amount consumed	communication. Task completion					Animal models are mostly behavioral, don't yet have neural underpinnings/lack validation.
Communication	Social transmission of information	social transmission of cookie jar	length of pairing, strain, genetics, life experience,	Latency to find food , successful transmission	communication. Task completion					
Communication	Social transmission of information	Vicarious freezing or bystander pain	mechanical responsiveness via Von Frey filaments, time spent freezing		communication. Task completion					
Cooperation/Coordination	Referred to in literature as cooperation/coordination	Chimpanzee chain pulling			Social cohesion					Not feasible to work in chimps. Model has limitation (e.g. solely based on reinforcement, limited translational relevance).
Cooperation/Coordination	Play behavior				Social cohesion					Most work is in young animals, decreasing priority for translational relevance. Rodents have play behavior restricted to early life, unlike other mammals, interesting model of syntax, basal ganglia function.

3. *Recommended models by human domain of concern.*

Table 3 includes recommended models of social systems by human domain of concern.

4. *Examples of successful use of animal paradigms to predict cognitive or behavioral outcomes in humans*

Table 3 includes animal paradigms prioritized as high, medium, and low multidimensional weighting; the high paradigms are the most relevant and ready for NASA applications given the level of knowledge about the neurocircuitry involved in the processes, their relevance for spaceflight, and their applicability for assessing the effects of radiation and other flight stressors and countermeasures.

5a. Can effects of human spaceflight stressors on social systems and processes outcome measures be tested in animal models such that combined effects of radiation and secondary stressors be evaluated?

Yes. Table 3 includes some animal models of the human constructs that have been assessed for their radiation sensitivity: social reinforcement (place conditioning, operant conditioning); social drive and motivation (social approach); defensive behaviors (single incident resident intruder; repeated psychosocial defeat stress); social discrimination (acquisition and retention of olfactory social discrimination); and social hierarchy (tube dominance test). These tests could be extended to characterize other stressors as well.

5b. Are there potential "reference stressors" that could be used as standards for assigning levels of significance to radiation-induced changes in social systems and processes that would guide translation of results to humans (e.g. equivalent blood alcohol levels, degree of sleep deprivation, etc.)? How would effects of reference stressor in social systems and processes best be measured in rodents and humans?

Yes. Reference stressors include oxidative stress (aging or obesity-related), micro-lesions in the central nervous system, and social stress-induced changes that could be used to assign levels of significance to radiation-induced changes in social system and processes. These would guide translation to humans as some of these measures can be compared between humans and animals.

Supporting biomarkers: Oxidative stress levels can be inferred in blood and non-central nervous system tissues in both rodents and humans, as well as in cultured pluripotent cells. Microlesions may be detectable via advanced imaging, although gaps remain in technology for resolving smaller rodent brains and even for microlesions in human brains. Social stress-induced changes in behavior are readily measured via behavioral measures (e.g. social interaction test) and serum measures (levels and time course of stress-induced hormones) in both rodents and humans.

5c. How well do animal model and human mission-relevant outcome measures of social systems and processes correlate?

As shown in Table 3, some of the animal models of the human constructs correlate quite well with human mission-relevant outcome measures. These human constructs include social reinforcement (place conditioning, operant conditioning); social drive and motivation (social approach); defensive behaviors (single incident resident intruder, repeated psychosocial defeat stress); social

discrimination (acquisition and retention of olfactory social discrimination); and social hierarchy (tube dominance test).

5d. Are current animal models of social systems and processes adequate or would research benefit from new or improved models?

Numerous animal models of social systems and processes provide insight into human constructs of social reinforcement, social drive and motivation, defensive behaviors, social hierarchy, and social discrimination. However, the field currently lacks animal models that unambiguously allow insight into human constructs of communication, sexual behavior, conspecific social conflict, emotional attachment, altruism, empathy, and cooperation/coordination.

5e. What are validation criteria for translatability and does the suite of identified models of social systems and processes provide sufficient cross validation of measured outcomes?

Although the group provided a general list of animal models with high translatability (Table 3), they strongly agreed that a suite of tests with standardized parameters is necessary for validation and cross-validation. The group strongly supported including validation criteria that are built into the experimental design rather than addressed *ad hoc* or *post hoc*.

5f. Is the use of multiple models of social systems and processes employing different approaches to provide converging evidence a requirement?

The use of multiple models of social systems and processes employing different approaches is preferred. However, to make such work cost- and time-effective, it is reasonable to employ a selection and a "meta-statistical" approach.

5g. What are the relevant translational models for social systems and processes from the Research Domain Criteria neurocircuitry systems?

Using the RDoC matrix (https://www.nimh.nih.gov/research-priorities/rdoc/constructs/ rdoc-matrix.shtml), the translational models provided in Table 3 assess the domains of negative and positive valence systems, as well as social processes. Performance in other domains (such as arousal) are influenced by these domains and can in turn influence performance in these domains.

5h. How can we identify and interpret underlying perturbations in functional neurocircuitry to assess complex cognitive processes relevant to social systems and processes?

The group believed that this area needs more work. However, advancements in induced manipulations of discrete cells populations and circuits (e.g. using optogenetic or chemogenetics) will enhance identification and interpretation of the underlying perturbations in functional neurocircuitry.

5i. What minimally invasive biomarker approaches (fluid-based, neuroimaging, etc.) would best support animal to human translation to study social systems and processes?

Although this is another area that requires additional study, fluid-based assessment of stress hormones and neuroimaging of microlesions and circuit activity are currently used.

5j. Can the effectiveness of countermeasures, including exercise, diet, pharmaceuticals, and training, be tested and validated in the identified suite of study social systems and processes models?

Yes. Countermeasures including diet, repeated cognitive training, and pharmacological interventions have been or can be used.

6. Gaps

A major gap is the use of "astronaut-like" animals for these tests (e.g. using animals that match the age-, sex-, and fitness-level of astronauts). Another gap is lack of knowledge of the neural perturbations that contribute to specific outcomes in some of the animal models, and the lack of a suite of biomarkers relevant to these tests in both animal models and humans. Finally, although the field has numerous animal models of social reinforcement, social drive and motivation, defensive behaviors, social hierarchy, and social discrimination, it currently lacks animal models that allow insight into human constructs of communication, sexual behavior, conspecific social conflict, emotional attachment, altruism, empathy, and cooperation/coordination. Ongoing discussion with NASA personnel in the HFBP Element would help prioritize the animal models used.

Session 4 Report: Translational Models of Neurocircuitry

Group 4 was tasked with reviewing translational models that have demonstrated regulation of neurocircuitry, and relationships between neurobiological and psychological mechanisms. The goal was to identify translational approaches that employ integrative models of neurocircuitry and incorporate multiple levels of analysis (e.g., molecular, cellular, physiological, social processes) to address potential biological control of behavior and performance.

1. *Summary*

Group 4 suggested that NASA

- combine stressor studies to include multiple comparisons to increase statistical power.
- expand current work to include altered or new techniques to improve models. Existing work has shown the existence of cognitive and neural alterations with space-relevant doses of radiation, but understanding this in more detail, and achieving good translation warrants these additions.
- consider strain effects within rodents and multiple converging tasks to demonstrate robustness.
- include NHP models to, at the least, examine the radiation dose or stressor exposure-response curves to provide a comparison with humans. The differences in neurobiology between rodents and humans may result in highly inaccurate predictions of the human response.
- use an approach that combines both targeted brain region and networks (e.g., hippocampus and frontal lobes) and that examines broader, whole-brain effects. The broader, whole-brain approach will identify previously missed targets and effects that may be more global or implicating very broad networks.
- include several neuroimaging techniques of humans and rodents in parallel to help bridge species. These images and their associations with behavioral tasks in humans and rodents, will help translation significantly.

1a. Recommended models that are well validated and can readily be adopted for use by NASA for experimental radiobiology.

The panel recommended establishing radiation dose-response curves for the paradigms listed below, and determining if the dose-responses are similar for animals and humans.

- Auditory-steady state response in conjunction with EEG
- Mismatch-negativity in conjunction with EEG
- Fluoro-deoxyglucose (FDG)-PET imaging - glucose metabolism to reflect brain function (metabolic activity modality of positron emission tomography)
- Translocator protein (TSPO)-PET imaging (glial activation; neuroinflammation)—marks activated microglia
- Diffusion tensor imaging modality of magnetic resonance imaging

- fMRI -functional magnetic resonance imaging
- MRI Spectroscopy (metabolic activity, e.g., inflammation)
- Behavior: pattern separation/mnemonic similarities
- Behavior: odor sequence task (known circuit?)

Are there any correlations with detrimental (or positive) behavioral effects?

- Perform analysis of multiple brain regions based on hippocampus, frontal cortex, perirhinal cortex, auditory cortex, occipital cortex, and basal ganglia (molecular and cellular)

1b. Areas where models are currently being used, but may require modification for use in NASA studies

- Use task probes rather than resting state (when possible)
- Use tasks that probe bigger networks. Use outcomes that engage distributed networks but then apply analytics to identify region specific responses to radiation exposure
- Electrophysiology in regions other than cortex; auditory brainstem responses to complex stimuli emerging measure with sensitivity to cognitive systems

1c. Areas where no models are currently available or where the models may be difficult to apply to NASA domains and/or countermeasure testing

- Studies must employ standardized protocols.
- EEG is a candidate method.
- Models must be reliable and results must be repeatable

2. *Consensus table of suggested outcome measures and models*

Table 4. *Group 4 recommendations for outcome measures and models to assess translational models of neurocircuitry*

Human Construct	Non-human Animal Construct	Paradigm/Tools	Translational neural systems (region, neurochemicals, radiological target, etc.)	Outcome Measure	Independent Variables	Operational Analog	Translatability	Notes (explains priority)	Other flight stressor sensitive?	Countermeasure sensitive?
Automatic Sensory Discrimination	Automatic Sensory Discrimination	Passive Auditory Oddball	fronto-temporal, source localization of radiation effects	EEG; Mismatch Negativity and P3a evoked potentials		EEG, in laboratory or in-flight	high	high translatability, widely studied in rodents, NHP, and humans in academic and pharma studies. Reflects the integrity of frontotemporal cortical networks that subserve higher cognitive processes. Pre-attentive/Passively evoked with very high test-retest reliability, response can be elicted in the absence of directed attention while subjects are engaged in other activities (e.g., operating a spacecraft). Strong links to cognitive, clinical, and psychosocial functioning. Well-established measures in preclinical and clinical in pharma translational drug development programs to determine acute CNS penetration, dose finding, and prediction of long-term cognitive effects. Also acutely sensitive to targeted non-pharmacologic cognitive training interventions.	Yes, sleep deprivation, hypoxia, head injury	yes
Sensory Registration and Coherence	Sensory Registration and Coherence	40-Hz Auditory Steady State Stimulation Paradigm	fronto-temporal, source localization of radiation effects	EEG; oscillations; Gamma band evoked power and phase synchronization; theta-gamma cross-frequency coupling		EEG, in laboratory or in-flight	high	high translatability, widely studied in rodents, NHP, and humans in academic and pharma studies. Reflects the capacity to generate synchronous responses to external stimulation, sensitive to frontotemporal cortical networks that subserve higher cognitive processes. Pre-attentive/passively evoked with high test retest reliability in 4 min. Strong links to cognitive, clinical, and psychosocial functioning. Well established measures in preclinical and clinical in pharma translational drug development programs to determine acute CNS penetration, dose finding, and prediction of long-term cognitive effects. Also acutely sensitive to targeted non-pharmacologic cognitive training interventions.	Yes, sleep deprivation, hypoxia? head injury?	yes
Brain Function	Brain Function	FDG-PET	Whole brain	Glucose metabolism	sex, genotype; radiation dose and post-irradiation duration	Pre- vs. post-flight FDG-PET	high	Highly translatable: FGD-PET has been shown to detect early changes in specific brain regions in early-to-late changes in humans with Alzheimer's disease. Assess dose- and time-dependent brain region-specific changes in brain function. Can be used longitudinally to monitor changes within individual animals. Caveat: resting state in animals (anesthesia)	Yes, fluid shifts, CO2 deprivation	Could be used to screen for countermeasures aimed at protecting brain function
Neuroinflammation	Neuroinflammation	TSPO-PET	Whole brain	microglial activation	sex, genotype; radiation dose and post-irradiation duration	Pre- vs. post-flight TSPO-PET	high	Highly translatable: TSPO-PET detects early changes in humans with Mild Cognitive Impairment (MCI) and age- and/or therapy-specific longitudinal changes in microglial activation in mice. Assess longitudinal dose- and time-dependent brain region-specific changes in neuroinflammation. Caveat: resting state in animals (anesthesia) Downstream readouts: cellular and molecular changes in brain including pathological and biochemical changes in immune cells, neurons/synapses, and inflammatory markers.	Yes, CO2 deprivation, head injury	Could be used to screen for countermeasures aimed at lowering inflammation
Memory	Memory	Pattern separation (rodent: Object-location cheeseboard; human: MST)	Hippocampus (dentate gyrus)	Behavior (task)	sex, radiation dose	Behavior (task)	High	The hippocampus and DG in particular have been shown to be particularly sensitive to radiation. These parallel measures in humans and rodents focus on DG function and have excellent test-retest behavioral reliability. They also provide control measures for attention, perception, etc. effects		
Memory & Executive function	Memory & Executive function	Odor/image sequence memory	Frontal-temporal	Behavior (task), ephys, fMRI	sex, radiation dose	Behavior (task)	High	Parallel task in rodents and humans showing excellent homology and common circuits (hippocampus and PFC) that are known to be affected by radiation. Behavior tied to functions needed in space		
Cell (macrophages) metabolic activity, cellular integrity, inflammation, & metabolite measures	Cell (macrophages) metabolic activity, cellular integrity, inflammation, & metabolite measures	MR spectroscopy (hyperpolarizing spectroscopic imaging)	whole brain and body	pyruvate metabolism in metabolic active cells	age, sex, genotype, radiation dose	pre-post flight	high	Highly translatable it is used in humans and rodents and is non-invasive. Provides neurobiological link between species. Caveat: unlike humans, animals will have to undergo anesthesia		yes
ELISA for blood inflammatory markers	ELISA for blood inflammatory markers	Mesoscale high sensitivity	whole body and brain	multiple cytokine and chemokine presence	sex, genotype; radiation dose and post-irradiation duration	longitudinal	high	highly translatable in humans and rodents and can help to build a prediction for other changes		yes
Brain connectivity integrity	Brain connectivity integrity	Diffusion-weighted imaging	Whtie and gray matter microstructure	DSI / ODF high-angular resolution models	sex, radiation dose	Pre-post flight?	high	Newer, high-angular and spatial resolution scans would provide whole-brain measures of potential inflammatory, vasculature, or neural structure changes		
Mechanisms of synaptic transmission, plasticity and connectivity in microcircuit e.g., CA3-CA1	Microcircuit integrity in isolated rodent neuronal network	in vitro electrophysiology in brain slices; extracellular recordings and patch-clamp:	hippocampus (dentate gyrus), mPFC, subiculum, perirhinal cortex, striatum, cerebellum	evoked field potentials, spontanous oscillations, presynaptic neurotransmitter release, synaptic and neuronal excitability	age, sex, post-irradiation interval, radiation dose, dose rate, energy, radiation species	post-exposure (post-flight) only - terminal procedure	medium	Limited to animal (freshly isloated) tissue only. In evolutionary conserved brain regions synaptic connectivity and mechanims are similar between humans and rodents (.eg. CA3-CA1 connectivity, AMPA-R, NMDA-R dependence etc.)	likely: microgravity, circadian effects	physical & mental exercise, antioxidants?
Sensori-motor adaptation	Sensori-motor adaptation	Vestibulo-ocular reflex gain and adaptation	brainstem and cerebellar function	eye movements in response to vestibular stimulation		In laboratory and in-flight		Highly translatable, previously monitored inflight, pre and postflight in humans.		Training paradigms, reduction of retinal slip paraidms/devices

Extended Summary:

Instead of providing individual answers to the questions posed by NASA, group 4 elected to provide an overview of their recommendations of translational models of neurocircuitry.

***Automatic Sensory Discrimination* can be tested in humans and animals** using Passive Auditory Oddball (An experimental design in which sequences of repetitive stimuli are infrequently interrupted by a deviant stimulus, and the subject's reaction to the deviant (oddball) stimulus is recorded). The outcome measure for this test would be EEG; Mismatch Negativity, and P3a evoked potentials. EEG can be measured in the laboratory or during spaceflight. This test is highly translatable and is widely studied in rodents, NHP, and humans in academic and pharmaceutical research studies. It reflects the integrity of frontotemporal cortical networks that subserve higher cognitive processes. The test is passively evoked with a very high test-retest reliability and responses can be elicited in the absence of directed attention while subjects are engaged in other activities (e.g., operating a spacecraft). EEGs have strong links to cognitive, clinical, and psychosocial functioning. The paradigm is a well-established measure in preclinical and clinical studies in "pharma" translational drug development programs to determine acute CNS penetration, effective dose detection, and to predict long-term cognitive effects. This test is also acutely sensitive to targeted non-pharmacologic cognitive training interventions, and is also sensitive to stressors such as sleep deprivation, hypoxia, and head injury and can be used to assess the effects of countermeasures.

***Sensory Registration and Coherence* can be tested in humans and animals**. The paradigm uses a 40-Hz auditory steady state stimulation paradigm and tests fronto-temporal activity as the source localization of radiation effects. The outcome measures are EEG-based and include oscillations, Gamma band evoked power and phase synchronization, and theta-gamma cross-frequency coupling. The test has high translatability, is widely studied in rodents, NHP, and humans in academic and pharma studies. The test reflects the capacity to generate synchronous responses to external stimulation and is sensitive to frontotemporal cortical networks that subserve higher cognitive processes. Signals are passively evoked with high test retest reliability in 4 min. There are strong links to cognitive, clinical, and psychosocial functioning. The test is a well-established measure in preclinical, clinical in pharma translational drug development programs to determine acute CNS penetration, dose finding, and to predict long-term cognitive effects. This test is also acutely sensitive to targeted non-pharmacologic cognitive training interventions and is sensitive to other flight stressor and potential countermeasures.

***Whole Brain Function* can be measured with FDG-PET to map glucose metabolism**. Numerous independent variables should be considered with this measure, such as sex, genotype, radiation dose, and post irradiation duration. Imaging could be performed in astronauts before and after a mission. The test is highly translatable: FGD-PET can detect early-to-late changes in specific brain regions in humans with Alzheimer's disease. It can assess spaceflight stressor exposure level- and time-dependent brain region-specific changes in brain function. It can be used longitudinally to monitor changes within individual animals. However, this test can only be administered in resting state in anesthetized animals. It is sensitive to other flight stressors such as elevated pCO_2, sleep deprivation, and head injury. Importantly, it could be used to screen for countermeasures aimed at lowering inflammation.

***Neuroinflammation* (especially activated microglia and macrophages) can be assessed in humans and animals**, and can be visualized in the whole brain with different techniques, both invasive and non-invasive such as TSPO-PET. (TSPO is a ligand for translocator protein, which is

expressed on activated microglia; see for example Vivash and O'Brien 2016). As with FDG-PET, TSPO-PET can be used to assess astronauts before and after a space mission, and can determine the effectiveness of countermeasures aimed at lowering inflammation. It is highly translatable: TSPO-PET detects early changes in humans with MCI, and age- and/or therapy-specific longitudinal changes in microglial activation in mice. These techniques can be used to assess longitudinal dose- and time-dependent brain region-specific changes in neuroinflammation. However, this test can only be administered in resting state in anesthetized animals. Downstream readouts: cellular and molecular changes in brain including pathological and biochemical changes in immune cells, neurons/synapses, and inflammatory markers.

***Hippocampal Memory* can readily be assessed in rodent models with the equivalent of the human construct.** The suggested paradigm is pattern separation (rodent: object-location cheeseboard; human: MST (mnemonic similarity task, cf. Kirwan & Stark, 2007; Yassa, Lacy, & Stark 2013). The operational analog is behavior or a task in astronauts and it is highly translatable. The hippocampus, and dentate gyrus (DG) in particular, have been shown to be particularly sensitive to radiation. These parallel measures in humans and rodents focus on DG function and have excellent test-retest behavioral reliability. They also provide control measures for effects on attention, perception, etc.

***Frontotemporal dependent Memory and Executive Functions* can be measured with odor sequence memory tests in rodents and humans.** This represent a parallel task in rodents and humans showing excellent homology and common circuits (hippocampus and prefrontal cortex) that are known to be affected by radiation. The behavior is tied to functions needed in space.

At a cellular level, research has identified measures of metabolic activity as indicators of cell integrity and inflammation in both humans and rodents. Magnetic spectroscopic imaging using ^{13}C MRSI of hyperpolarized [1-^{13}C] pyruvate (e.g. https://doi.org/10.1371/journal.pone.0087031). Notably ^{13}C MRSI is a non-invasive metabolic imaging method widely used in the cancer field to measure cell metabolic activity that can also be used to measure macrophage and microglia metabolic activity. Magnetic resonance spectroscopy (MRS) can be used to measure whole brain and body non-invasively. The specific outcome measure is pyruvic acid metabolic conversion to lactic acid in metabolically active cells. It can be used pre and post flight and also to test countermeasures that affect inflammation. Highly translatable, it is used in humans and rodents and is non-invasive. It provides neurobiological links between species. Caveat: unlike humans, animals will have to undergo anesthesia. An example of its use in traumatic brain injury is at: https://www.nature.com/articles/s41598-017-17758-4.

At the cellular level there are other outcome measures which can be identified across human and non-human constructs. For instance, there are highly sensitive enzyme-linked immunosorbent assays (ELISAs) for blood inflammatory markers in small volumes in the form of multiplex bead systems (e.g. Mesoscale™ and Simoa™). This technique can identify changes in the whole body and brain with the outcome measure being multiple cytokines and chemokines. And it can be used as a longitudinal measure in operational analog. Highly translatable in humans and rodents and can help to build a prediction for other changes.

Brain Connectivity Integrity can be measured in human and non-human by the use of diffusion weighted magnetic resonance imaging and can assess white and grey matter microstructure. Diffusion spectrum imaging and orientation distribution function imaging have high angular resolution and can be used post flight as necessary. Newer, high-angular and spatial

resolution scans would provide whole-brain measures of potential inflammatory, vasculature, or neural structure changes.

To mimic what in humans would be mechanisms of synaptic transmission, plasticity and connectivity in microcircuit e.g., CA3-CA1 (hippocampus fields), we can look at microcircuit integrity in isolated rodent neuronal networks by the use of in vitro electrophysiology in brain slices; extracellular recordings and patch-clamp. With these techniques we can assess hippocampal, medial prefrontal cortex, subiculum, perirhinal cortex, striatum and cerebellum functions. The specific outcome measures would be evoked field potentials, spontaneous oscillations, presynaptic neurotransmitter release, synaptic and neuronal excitability. This is a terminal procedure and can only be used in rodents post flight or post radiation exposure. It is limited to animal (freshly isolated) tissue only. In evolutionary conserved brain regions, synaptic connectivity and mechanism are similar between humans and rodents (e.g. CA3-CA1 connectivity, AMPA receptor, NMDA receptor dependence, etc. [glutamate receptor ion channels]). It is sensitive to other in-flight stressor such as microgravity and circadian effects.

Sensory-Motor Adaptation is one more element common to human and non-human constructs which we identified as a promising translational model. This paradigm assesses the vestibular-ocular reflex and its gain and adaptation reflecting brainstem and cerebellar function. The specific outcome measures are readily measured as eye movements in response to a vestibular stimulation. This can be measured in the laboratory and in flight and consequently is highly translatable. It has been previously monitored inflight and can be monitored pre-and post-flight as well in humans.

Summary of Major Conclusions and Recommendations from the Four Breakout Session Participants

The following narrative summarizes the major findings and combined recommendations from the participants.

1. A number of valuable animal (rodent) behavioral models, including cognitive, affective, and social behaviors, are currently being used to characterize the effects of space-like radiation on the brain. These models have the appropriate sensitivity to detect responses from mission-equivalent radiation doses and many have been validated independently for their ability to predict effects of drugs and pathophysiology of diseases such as schizophrenia, major depressive disorder, and autism, supporting mechanistic similarities and validating translatability to humans. The numerous models for different cognitive and behavioral domains are detailed in this workshop report.

2. A few additional models may enhance the fidelity and sensitivity of current investigations, especially when used concurrently. Biochemical measures, electrophysiological (e.g. EEG) parameters during task performance, and imaging (especially functional imaging) would complement behavioral measures, validate mechanistic similarities between animals and humans, and provide benchmark biomarkers for inter-species scaling.

3. Models currently in use, in combination with the recommended additional models, could address the effects of non-radiation spaceflight stressors such as altered gravity, sleep deprivation, circadian dysregulation, and isolation and confinement. Priority should be given to adapting current models and organizing them into batteries of tests to evaluate operationally relevant behaviors and the effects of combined stressors.

4. Models currently in use, along with the others identified during the workshop, could assess the effectiveness of countermeasures and mitigation strategies. The precipitants provided an evaluation of countermeasures, which is included in this workshop report.

5. Many experimental parameters should be standardized, whenever practical, to facilitate inter-comparison of results. These parameters include exposure conditions (radiation and other stressors), animal species, strain, age, sex, post exposure evaluation times, animal husbandry conditions.

6. Spaceflight stressors should be assessed using a battery of well-vetted tests that sample as many neuropsychological domains as practical. An optimal approach would target brain regions and networks (e.g., hippocampus and frontal lobes) and examine broader whole-brain effects. A broader whole-brain approach would identify previously missed targets and assess effects that may be more global or implicate very broad networks.

7. The panels recognized that valid and reliable reference stressors for studying central nervous system (CNS) effects of spaceflight-like impairment in translation models are needed. Traumatic brain injury is a diffuse injury model that has some pathophysiology properties similar to radiation exposure effects. Manipulating serotonin levels (which can induce human depression) may be a novel method to probe analogous spaceflight outcomes in animals; aging or obesity-related oxidative stress, microlesions in CNS, and social stress measures could be used to establish reference values. However, stress is difficult to standardize across species and humans may anticipate treatments while animals do not; which would

differentially affect the reactions to experimental manipulations. The use of reference stressors such as blood alcohol levels was considered useful for communication of impairment but subject to non-linear exposure-responses and therefore may not be reliable but traumatic brain injury was suggested as an analog for comparison.

8. Alterations in performance should be evaluated on an individual basis in animals that have been preselected for their suitable or superior baseline performance to better emulate high-performing human populations (astronauts). Deviations from "normal" need to incorporate aspects of what is "normal" for each individual and studies may benefit from evaluation of patterns of behaviors in repeated measure designs. Further refinements in models might include "astronaut-like" physically fit animals that have been prescreened for top tier performers in several domains, are age appropriate, and include both sexes. Such refinements might also include testing during active (awake) phase when practical and including some outbred strains to address inter-individual variability.

9. Individual performance that deviates from cohort averages in test batteries (e.g., converting individual performance scores to Z-scores or non-parametric equivalents) could be used as quantitative measures to compare the magnitudes of changes in animal and human performance elicited by stressors.

10. No consensus was reached on the use of non-human primates. Although, rodent models might not be adequate for evaluation of very complex mental functions such as abstraction and concept formation, rodent models will suffice for most purposes and the use of higher species, if needed, should focus on a small, specific set of questions—not a broad survey.

11. The overall strategy of using assessment tools to link operational requirements for mission relevant tasks to permissible outcome levels in humans, and then to permissible exposure levels in animal analogs of human performance was considered valid.

The following four tables summarize a set of translational models of human cognition (Table 5) assessment measures for non-cognitive behaviors (Table 6), assessment measures for social systems and processes (Table 7), and examples of models that have been validated for their ability to predict human outcome measures (Table 8).

Table 5. *A recommended set of translational models of human cognition.*

Human Construct	*Recommended Rodent Model*
Fit for duty standard	Rodent 5-Test; (4 cognitive domains, 1 psychosocial)Needs to be developed. Would require consortium
Vigilant attention	Rodent psychomotor vigilance test
Psychomotor vigilance (PVT)	5 choice continuous performance test (5C-CPT)
Working memory	Odor span test
Fractal 2-back (F3B)	Delayed (non) match to sample test
Risk decision-making	Barrus and Winstanley assay
Balloon analog risk (BART)	Rodent Iowa gambling task
Spatial learning and memory	Touchscreen cognitive testing (Bussey et al. 2008). Morris water maze and Barnes maze (but not necessarily correlated to visual object learning test (VOLT)
Visual object learning (VOLT)	
Perceptual executive functions	Operant set-shifting
Abstraction, concept formation	Rodent attentional set shifting test (intra and extradimensional shifting)
Abstract matching (AM)	
Metacognition	Post-decision wagering, etc. Kepecs
Unconstrained cognitive flexibility	Unconstrained cognitive flexibility test (Hecht)

Table 6. *Candidate assessment measures for non-cognitive behaviors.*

Assessment Measure
Immobilization stress (plasma corticosterone levels, HPA axis as measures of stress response; but some concerns this may not be reliable measure at low radiation doses).
Measures of anxiety/avoidance (light dark box without elevation)
Learned fear, fear inhibition, fear generalization (acquisition and extinction of learned fear as measured by freezing, operant, or startle behaviors)
Explorative behavior and measures of anxiety in open areas (open field, light dark box) and elevated anxiety provoking areas (elevated zero maze, elevated plus maze)
Reward processing, anhedonia (sucrose preference test, intracranial stimulation), does not require ambulation
Depressive behaviors (forced swim and tail suspension tests)
Chronic stress to model small space environments (cage size modification), analog to HERA

HPA= hypothalamic-pituitary-adrenal; HERA=human exploration research analog; SSRI=selective serotonin reuptake inhibitors

Table 7. *High priority models of social systems and processes (avoidance, withdrawal, etc.)*

Human Construct	Animal Contract	Assessment Measure	Independent Variables	Outcome Measure	Operational Analog
Social Reinforcement	Social Reinforcement	Place Conditioning	Familiarity (conspecific, cage mate), sex, estrus female, offspring	Latency to approach, time spent, extinction, reinstatement	Proximity, shared social activities, content analysis
		Operant Conditioning	Familiarity (conspecific, cage mate), sex, estrus female, offspring, schedule	Breakpoint, response rate, demand intensity, demand elasticity	Proximity, shared social activities, content analysis
Social Drive or Motivation	Social Drive or Motivation	Social Approach	Familiarity (conspecific, cage mate), sex, estrus cycle	Latency to approach, time spent,	Proximity, shared social activities, content analysis
Defensive Behaviors	Social Avoidance /Aggression	Resident intruder (one time)	Familiarity (conspecific, cage mate), sex, estrus cycle, length/complexity of residence	Latency to approach, time spent, latency to attach, number of attacks, severity of attack	Response to conflict
		Psychosocial Defeat Stress	Stain, sex, age, estrus cycle, length/complexity of residence, sensory contact during adjacent living, number/intensity of defeat bouts	Latency to approach, time spent, latency to attach, number of attacks, severity of attack, social interaction response (approach avoid)	Response to conflict
Social Discrimination	Social Discrimination: affiliative vs antagonistic	Olfactory Social Discrimination	Target (social vs nonsocial), exploration time	Latency, duration, proportion of sniffing, habituation over time, dishabituation, discrimination index	Social cohesion
	Social Recognition Memory	Olfactory Social Discrimination with Retention Interval	Familiarity (conspecific, cagemate), target (social vs nonsocial)	Latency, duration, proportion of sniffing, habituation over time, dishabituation, discrimination index	Social cohesion
Social Hierarchy	Social Dominance	Tube test (tube of water)	Length of pairing, strain, genetics, life experience, coping biases, barbering of cage mates	Win probability, latency to win	Conflict, group living

Table 8. *Examples of successful translation validation*.

Animal Model/Test	*Prediction of Behavioral Outcome in Humans*
Elevated plus maze and elevated zero maze	Anxiolytic effects, for example benzodiazepines
Forced swim test	Anti-depressive effects, for example SSRIs and ketamine
Spatial navigation	Spatial navigation—direct analog
Fear conditioning and extinction	d-cycloserine; post-trauma or prior memory testing administration of glucose to activate hippocampus and contextual learning
Object recognition	Age-related cognitive decline; mild cognitive decline (MCD; neurogenerative conditions and dementias
Sleep deprivation manipulation in conjunction with performance test(s)	Sleep deprivation test

Unresolved Questions and Issues

1. The most suitable method for *quantitatively* translating animal and human behavior was not identified. A potential approach could use Z-scores or equivalents based on the results of composite test batteries to compare the magnitudes of deviations from cohort averages. It is not known whether graded exposure levels to stressors (radiation doses, hours of sleep deprivation, etc.) would elicit linear or non-linear responses or how combinations of stressors would interact.

2. The definition of "significance" with respect to impairment in mission performance requirements was not adequately characterized. Some quantitative criteria such as changes in reaction time or error rate in task performance are needed. Furthermore, prioritizing the most important mission tasks and evaluation measures is important for cost-effective management of risks.

3. Although spaceflight stressors induce many changes in performance, whether the changes are considered beneficial or deleterious will depend on the task. For example, reduced distractibility could be interpreted as beneficial for vigilant attention but deleterious in terms of awareness in detecting unexpected anomalies.

4. What compensatory mechanisms does the CNS use to maintain homeostasis during spaceflight? Are the mechanisms the same in animals and humans, or do humans have more options or a greater capacity to adapt than animals (e.g. cognitive reserve), giving them a higher tolerance to stressors?

5. What are the underlying networks and mechanisms that result in altered behavioral performance, compensation, and adaptation (brain performance pathways)? Are they the same for animals and humans? Can this information be used to design countermeasure strategies?

6. Sensorimotor performance and responses to spaceflight stressors were not evaluated by this workshop panel but were addressed in a subsequent NASA workshop held in 2018.

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Appendixes

Appendix A: Meeting Agenda

Optimization of Translational Animal Models to Assess Human Spaceflight Performance for Studying the In-Flight Effects of Space Radiation:
The Journey to Mars and Back

NASA Workshop sponsored by the NASA Human Research Program's Space Radiation Element and the Human Factors and Behavioral Performance Element
South Shore Harbour Resort & Conference Center, League City, TX
June 13-14, 2017

Tuesday, June 13, 2017

7:00 - 8:00 AM	Registration
8:00 - 8:10 AM	**Welcome Remarks** (Amphitheater) - Lisa Simonsen Venue Information - Suzanne Miller
8:10 - 8:35 AM	**Overview of behavior and cognitive domains important to spaceflight** - Tom Williams
8:35 – 9:00 AM	**Overview of behavior and cognitive domains evaluated for effects of radiation** - Greg Nelson
9:00 - 9:15 AM	*Break*
9:15 - 10:00 AM	**Executive summary of the human-to-animal mapping matrix for high priority domains** (Amphitheater) - Richard Britten
10:00 - 10:15 AM	**Charge to Breakout Sessions** - Greg Nelson
10:15-10:30 AM	*Break*
10:30 – 12:00 Noon	**Invited Presentations** (Amphitheater)
12:00 – 1:00 PM	*Lunch at Paradise Reef Restaurant*
1:00 – 4:00 PM	**Breakout Sessions** Session 1: Amphitheater Session 2: Pier Room Session 3: Steuben Room

Session 4: Waterford Room

4:00 – 5:00 PM **Group Discussion & Progress Status** (Amphitheater)

6:00 PM *Group dinner at Landry's Seafood Restaurant*
Address: #1 Kemah Boardwalk, Kemah, TX 77565

South Shore Harbour Resort & Conference Center, League City, TX
June 13-14, 2017

Wednesday, June 14, 2017

8:00 – 8:50 AM **Group Session Status** (Amphitheater)

8:50 - 9:10 AM **Group Photo**

9:10 – 11:30 AM **Breakout Sessions** (Continued)
Session 1: Amphitheater
Session 2: Pier Room
Session 3: Steuben Room
Session 4: Waterford Room

11:30 – 12:30 PM *Lunch at Paradise Reef Restaurant*

12:30 – 1:30 PM **Report Out and Group Discussion** (Amphitheater)

1:30 – 2:00 PM **Future Directions and Next Steps** - Lisa Simonsen

2:00PM *Adjourn*

Group Photo

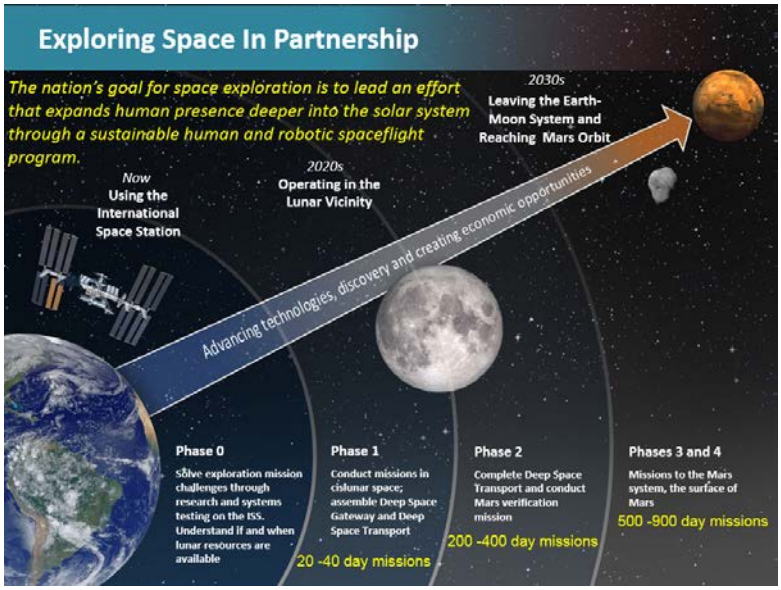
Back row, left to right. Amelia Eisch, PhD; Lawrence Tecott, MD, PhD; Ruben Gur, PhD; Robert Turner, PhD; Roman Vlkolinsky, PhD; Jacob Raber, PhD; LTC Matthew Hoefer, DO; Richard Britten, PhD; Raphael Rose, PhD; Pete Roma, PhD; Catherine Davis, PhD; Holly Moore, PhD; Jared Young, PhD.
Front row, left to right. Charles Limoli, PhD; Victoria Risbrough, PhD; Cynthia Lemere, PhD; Susanna Rosi, PhD; Bernard Rabin, PhD; Jamie Zeitzer, PhD; Craig Stark, PhD; Gregory Light, PhD.

Appendix B: Presentations

Presentation 1

Lisa C. Simonsen, PhD.
Space Radiation Element Scientist
NASA Langley Research Center

1. ***NASA's Mission. The nation's goal for space exploration is to lead an effort that expands human presence deeper into the solar system through a sustainable human and robotic spaceflight program.***



2. ***The current NASA exploration plans call for a phased approach that focuses on operations in cis-lunar space before moving to Mars missions.***

3. ***There are 5 primary hazards to humans during space flight, each with different health consequences or risks.***

Decreased gravity
- *Bone Loss, Muscle Atrophy, Reduced Immune Function, Fluid-Shifts*

Isolation/confinement/altered light-dark cycles
- *Sleep Issues, Psychological Stress*

Hostile/closed environment
- *Atmosphere, Microbes, Dust, Habitability*

Distance from Earth
- *Autonomy, Food Systems/Nutrition, Clinical Medicine*

Increased radiation
- *Cancer, CNS, Cardiovascular and Degenerative Changes, Acute Risks*

4. ***Today's astronauts*** are healthy individuals (never-smokers, healthy diet, normal weight) who average 35-55 years old with first mission assignments (ISS) at 47 years old. The current corp is 70% male and 30% female.

5. ***Workshop Goal***

Develop a consensus test battery of cognitive and behavioral tests and associated biomarkers that:
- Support the translation of animal models to humans
- Are conducive to testing decrements due to radiation and other spaceflight stressors
- Are suitable for evaluating mission acceptable countermeasures

6. ***Workshop Deliverables***

Report on the use of standardized assessment tools for analogous rodent and human behavior and performance parameters that may be used to assess in-mission risks of potential CNS decrements due to radiation exposure.

Report should be organized into five major sections including:
– Consensus table of outcome measures & models
– Assessment of those models relevant to:
  • Cognitive Performance & Circadian Dysregulation
  • Neurobehavioral Performance
  • Social Systems and Processes
  • Neurocircuitry via neurobiological and psychological mechanisms
  • Session moderators will coordinate written input from their panels

7. *Questions to interrogate validity of proposed model systems*

- Can effects of human spaceflight stressors on cognitive and behavioral outcome measures be tested in animal models such that combined effects of radiation and secondary stressors be evaluated?
- Are there potential "reference stressors" that could be used as standards for assigning levels of significance to radiation-induced changes that would guide translation of results to humans (e.g. equivalent blood alcohol levels, degree of sleep deprivation, etc.)? How would effects of reference stressor best be measured in rodents and humans?
- How well do animal model and human mission-relevant outcome measures correlate?
- Are current animal models adequate or would research benefit from new or improved models?
- What are validation criteria for translatability and does the suite of identified models provide sufficient cross validation of measured outcomes?
- Is the use of multiple models employing different approaches to provide converging evidence a requirement?
- What minimally-invasive biomarker approaches (fluid-based, neuroimaging, etc.) would best support animal to human translation?
- Can the effectiveness of countermeasures, including exercise, diet, pharmaceuticals, and training, be tested and validated in the identified suite of models?

8. Workshop Agenda

Agenda is presented in Appendix A

Presentation 2

Space Radiation/Human Health and Behavioral Performance (HFBP) Workshop: Cognitive and Behavioral Domains

Thomas J. Williams, PhD
Human Factors Behavior and Performance Element Scientist

1. ***Overview of Human Research Program (HRP)***

2. ***Human Research Program Purpose.***

- HRP is responsible for conducting research to enable space exploration.
- Human travelers to Mars will experience unprecedented physiological, environmental, and psychosocial challenges that could lead to significant health and performance decrements in the absence of effective mitigation strategies.
- Mission success will depend on ability to develop and implement mitigation and countermeasure strategies.

3. ***Primary hazards for human system risks.***

- Altered gravity (hyper, hypo, transitions)
  - Effects on: bone, muscle, cardiovascular system, sensorimotor system, nutrition, behavior/performance, immune function, human factors and clinical medicine.
- Radiation (low Earth orbit, deep space)
  - Carcinogenesis, immune function, behavior/performance, late tissue degeneration, pharmaceutical stability
- Distance from Earth (medical care impacts)
  - Behavior/performance, autonomy, food systems, clinical medicine
- Isolation (psychological)
  - Behavior/performance
- Hostile/closed environment (spacecraft design)
  - Behavior/performance, nutrition, immune function, toxicology, microbiology

4. ***Human Research Program (HRP) Goal***

Provide human health and performance countermeasures, knowledge, technologies, and tools to enable safe, reliable, and productive human space exploration.

5. ***Rationale to employ standard measures in health care***

"The use of standard measures offers the opportunity to efficiently identify conditions that may modify diagnoses and treatment plans and renders the information usable by various systems for various purposes"

Reference: Patients in context – HER Capture of social and behavioral determinants of health. Adler NE, Stead WW. New England J Medicine Feb 19, 2015

6. ***Example of standard measures: Social and Behavioral Domains and Measures***

Table from Adler NE, Stead WW. New England J Medicine Feb 19, 2015

7. ***Why Behavioral Health and Performance Standard Measures?***

- Facilitate integrated assessment & understanding
- Identify & characterize risk across: settings, missions, disciplines (relationships among multiple systems)
- Expand capacity: more sensitive/specific identification of: "space normal"
- Better define and tailor countermeasures (Precision medicine)
- Psychosocial "vital signs"

8. ***Future 1 year mission program***

- HRP is proposing a coordinated program of 1 year missions, taxi flights, and 6-month missions
- Conduct same measures at 3 discrete durations
- Larger n, increases confidence in 1 year mission data
- May observe early changes in adaptation not noticed previously

9. ***Mission Unknowns***

Dynamics/time courses of physiological changes are complex

10. ***Behavioral Health and Performance. Purpose & Risks***

Manage and mitigate the behavioral health and performance risks associated with space travel, exploration and return to terrestrial life

- Risk of adverse cognitive & behavioral conditions and psychiatric disorders
- Risk of performance and behavioral health decrements due to inadequate cooperation, coordination, communication and psychosocial adaptation within a team

- Risk of performance decrements and adverse health outcomes resulting from sleep loss, circadian de-synchronization, and work overload

11. ***Behavioral Medicine Statement & Status***

Full Title: Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders

Risk Statement:
Given the extended duration of current and future missions and the isolated, confined and extreme environments, there is a possibility that

(a) adverse cognitive or behavioral conditions will occur affecting crew health and performance; and
(b) mental disorders could develop should adverse behavioral conditions be undetected and unmitigated.

12. ***Risk Overview: BMed Risk Gaps***

1. We need to identify and validate countermeasures that promote individual behavioral health and performance during exploration class missions.

2. We need to identify and validate measures to monitor behavioral health and performance and determine acceptable thresholds to these measures during exploration class missions.

3. We need to identify and quantify the key threats to and promoters of mission relevant behavioral health and performance during exploration class missions.

5. We need to identify and validate measures that can be used for the selection of individuals that are highly resilient to the key behavioral health and performance threats during exploration class missions.

6. We need to identify and validate effective treatments for adverse behavioral conditions and psychiatric disorders during exploration class missions.

7. We need to identify and validate effective methods for modifying the habitable vehicle/ environment to mitigate the psychological and behavioral effects of psychological environmental stressors (e.g. isolation, confinement, reduced sensory stimulation) likely to be experienced in exploration class missions.

8. how personal relations/interactions (family, friends and colleagues) affect astronauts' behavioral health and performance during exploration class missions.

9. We need to understand long term astronaut health for long duration exploration missions and find the best methods to promote long term post mission behavioral health.

13. ***Behavioral Health and Performance Standard Measures***

Why? To establish a common set of measures for use in spaceflight and analog research to: develop baselines, systematically characterize risk likelihood and consequences, and assess countermeasure effectiveness

14. ***Behavioral Health and Performance Standard Measures & Habitability***

Psychological Factors relevant to success of mission

- *Individual* (adaptation and performance)
  - Personality
  - Motivation
  - Visual/Perceptual Processing
- *Group* (small groups in confined quarters)
  - Psychosocial factors
  - Reduce interpersonal conflict/conflict resolution
  - Decrease risk of psychological problems
- *Environmental*
  - Social organizational
    - Meaningfulness/division of labor
    - Intellectual challenge/Avoiding boredom
  - Design (harmonious group living)
    - Privacy
    - Habitability (sleep areas
    - Social (interpersonal connectedness in flight, back to earth)
    -

15. ***Risk Overview: BMed Risk Key Terms***

- *Cognition:* internal mental processes
- *Behavior:* externally observable actions or responses
- *Stress:* reaction to a stimulus that disturbs the physical or mental equilibrium
- *Resilience:* ability to adjust easily to or recover from stress, change, or difficulty
- *Well-being:* the presence of positive emotions and moods (e.g., contentment, happiness), the absence of negative emotions (e.g., depression, anxiety), satisfaction with life, sense of control, fulfillment, and positive functioning
-

16. ***BMed Problems in Spaceflight***

17. ***Behavioral Health and Performance Standard Measures***

Behavioral Core Measures NRA

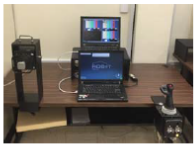
Implement validated measures to assess cognition, operational performance, well being, team cohesion, sleep and circadian phase



- **Cognition** (Vigilant attention, psychomotor speed, lapses of attention, impulsivity, etc.)
- **Neurobehavioral signs of stress & fatigue** (mental & physical) using Visual Analog Scales (VAS)
- **Personality** ("Big Five Factors")
- **Journals**
- **Team cohesion vs conflict**
- **Actigraphy** (acitivity/wake cycles)
- **ROBoT** (operational performance task)

Cognition Test Battery


Lexical Indicators


ROBoT

HRP Standard Measures

- Covers all HRP risks
- Allows comparison of 6 & 12 month ISS missions

- Cognition
- Neurobehavioral assessments using VAS
- Team cohesion vs conflict
- Actigraphy
- ROBoT
- Additional measures as appropriate (e.g., personality factors related to spaceflight adaptability)


Sleep-Wake Actigraphy


Sociometric Badges

19

18. ***Examples of BMed problems encountered on Russian Salyut & Mir missions***

- Soyuz T10-Salyut 7 (1984): Crew reported hallucinations to mission control.
- Soyuz T14-Salyut 7 (1985): Depression may have contributed to evacuation and early termination of mission.
- 2 of 7 (29%) of NASA Shuttle-Mir astronauts reported depressive symptoms.

References:

Buckey, J. C., Jr. (2006). *Space Physiology*. Oxford University Press.
Troitsyna, M. (2011, June 14). Angels in space nothing but top secret hallucinations. *Pravda*.
Burrough, B. (1998). *Dragonfly*. HarperCollins.

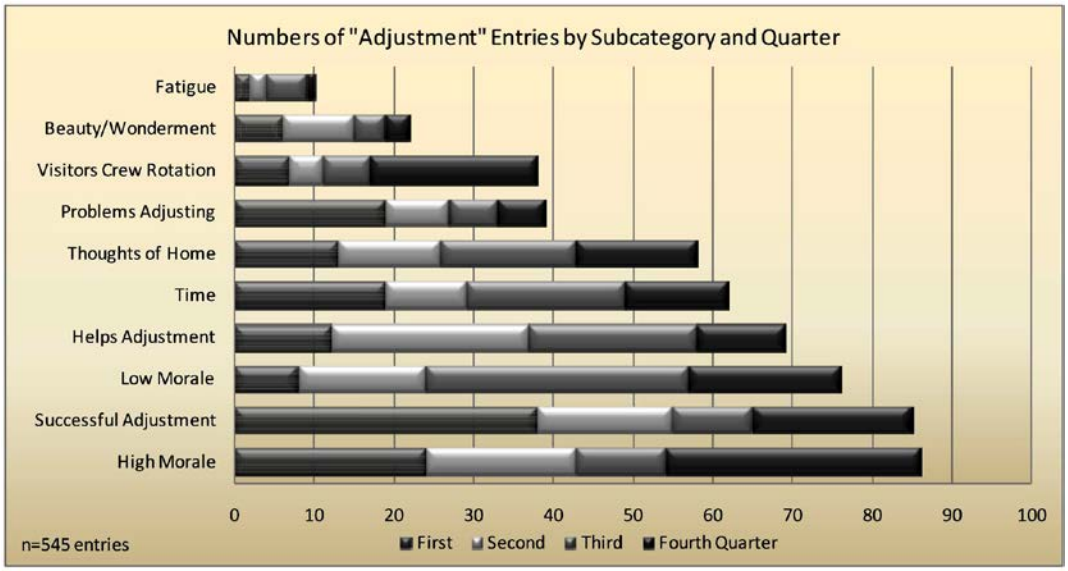
19. ***Examples of BMed problems encountered on ~ 90 day Skylab missions***

"Thus, on 27 December 1973, the Skylab 4 astronauts conducted a daylong "sit-down strike." Cooper described the crew pejoratively as hostile, irritable, and down-right grumpy."
Astronaut Journals (ISS)

Reference: Vakoch, D. A. (2012). *Psychology of Space Exploration: Contemporary Research in Historical Perspective*. National Aeronautics and Space Administration Headquarters.

20. ***J Stuster has conducted a review of astronaut journals*** *to identify psychosocial issues emerging during long ISS spaceflights and found patterns of behavior with stage of mission.*

Stuster J. (2010) *Behavioral Issues Associated with Long-Duration Space Expeditions: Review and Analysis of Astronaut Journals --Experiment 01-E104 (Journals): Final Report*, NASA Technical Document, TM-2010-216130



21. ***Example journal entries:***

- I hesitate to use the word "depression," but it seems an appropriate description of my mood lately. Nothing seems to cheer me up much.
- Just feeling downright grumpy today. At lunch I was throwing food away because I was frustrated with how it is packed and organized. Later I was complaining about how the water sampling procedures were organized.
- I've been feeling slightly depressed lately, which I sort of measure by my inability to get going on a number of personal projects that I really need to make headway on. Today would have been a good opportunity.
- I had some free time. But I just couldn't force myself to work on anything (beyond what I was required to do for my job).

Most astronauts self-reported stress increases with time in 6-month ISS missions. This has been confirmed by analysis of self-reports of stress by D. Dinges, et al.

22. ***The Research Domain Criteria (RDoC) initiative*** by the National Institute of Mental Health is enhancing the study of mental health disorders and provides a valuable research framework. It is described in the 2008 NIMH Strategic Plan and the NIH August 2016 report "Behavioral Assessment Methods for RDOC Constructs.

• "Objectives include redefining mental disorders into observable and measurable components that are more closely aligned with the biology of the brain; fostering broad sharing of data and resources [supporting] researchers in ways that inspire creativity and innovation"

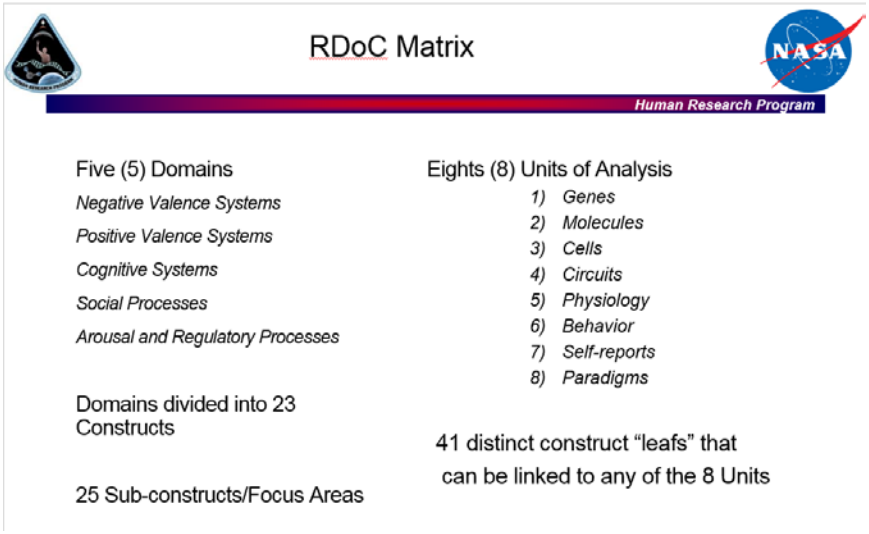
• Explicitly based on premise that mental disorders are *disorders of brain circuits*

• “The tools of clinical neuroscience [...] can be used to identify dysfunction in neural circuits” (Morris & Cuthbert 2012)

• Goal to support translational neuroscience in mental health research

NASA is evaluating the RDoC framework for its own use.

23. ***NIMH Research Domain Criteria (RDoC) Matrix***



24. ***Several biomarker studies*** are ongoing in response to BMed needs and use laboratory conditions or space flight analog facilities such as the ground based HERA spacecraft mock-up.

Biomarkers as Predictors of Resiliency and Susceptibility to Stress in Space Flight
PI: Namni Goel, PhD, University of Pennsylvania
• Analogs: HERA & Hi-SEAS

• High stress and total sleep deprivation

• Cardiovascular, Cortisol, Catecholamines, C Reactive Protein, Metabolomics, MicroRNA markers, Neurocognitive Performance

Markers of Susceptibility to Neurobehavioral Decrements in Space Flight
PI: David Dinges, PhD, University of Pennsylvania
• Laboratory (Retrospective and Prospective)

• Partial and total sleep deprivation

• Arterial spin labeling (ASL), Heart rate variability (HRV), α-amylase, Genetic alleles (sleep related), Neurocognitive Performance

Development and testing of biomarkers to determine individual astronauts’ vulnerabilities to behavioral health disruptions

Steven W. Lockley, PhD, and Charles A. Czeisler PhD, MD, Brigham & Women's Hospital, and Harvard Medical School

• Retrospective (Phoenix Lander, Mission Control, Shuttle, ISS etc), Laboratory, & Antarctic

• Sleep deprivation & circadian asynchrony

• Actigraphy, EEG, ECG, Cortisol, Catecholamines, Metabolomics, Lipidomics,

Immune Markers, Neurocognitive Performance

25. ***An important analog study*** is being conducted jointly by NASA and the European Space Agency: "Neurostructural, Cognitive, and Physiological Changes During a 1-year Antarctic Winter-Over Mission". PI. Mathias Basner, MD, PhD, U. Pennsylvania School of Medicine

Aims

Investigate changes in crewmembers participating in an Antarctic winter-over mission using crew from several Antarctic stations:

• Neurostructural and neurofunctional/cognitive performance.

• Sleep duration, sleep-wake rhythms, and light exposure.

• Heart rate, heart rate variability, and sleep structure.

• Mood, fatigue, health, energy, stress, workload, sleep quality, conflicts, and crew cohesion.

Measures:

• Cognition battery (cognitive performance)

• Actigraphy (sleep/wake, proximity)

• ECG (heart rate)

• PVT-B (psychomotor vigilance)

• Questionnaires (affect)

Photo: Concordia Antarctic Station

26. ***Identification and use of translational animal models***

Several initiatives have wrestled with the problem of identifying and using animal models to predict human nervous system responses. A recent example is a National Academies of Science Institute of Medicine Report "Improving the Utility and Translation of Animal Models for Nervous System Disorders" 2012. The report discusses differences in human & non-human species, faulty experimental designs, questionable statistical analyses and other issues and may provide guidance for this workshop.

27. ***Challenges of Standard Measures***

- Cultural change ("frames of thinking")
  - Social & behavioral determinants
- "Standard" exists…

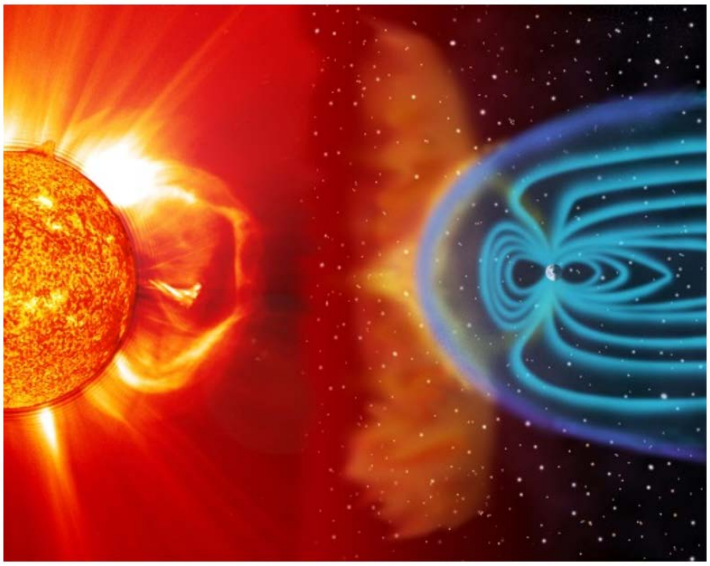
    - Available
    - Useful (valid & reliable)
    - Feasible & acceptable (to measure & to know)
        - Not available from other sources (unobtrusive measures)
- Privacy vs operational mission
    - Not overly sensitive to ask
    - Operational relevance vs research “interests”
- Added demands: elusive “Gold standard”
- Sensitivity/specificity of data (continuum)
    - Lab result vs psychological “result”
    - Monitoring vs intervention

Presentation 3

Space Radiation and Responses of Animal CNS

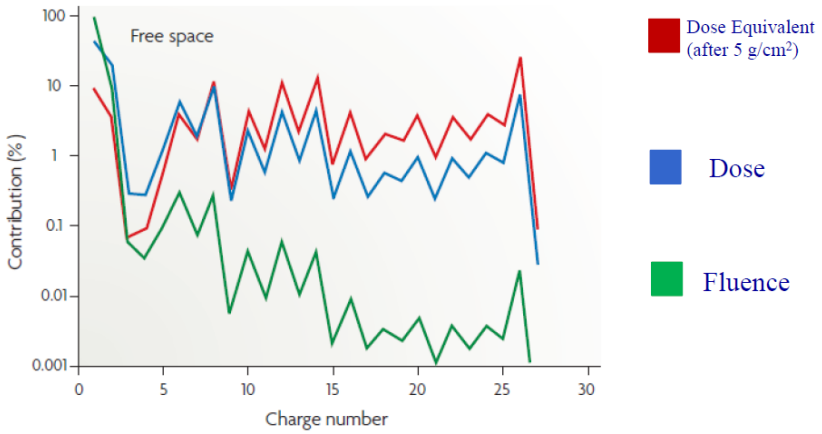
Gregory Nelson, Ph.D.
Loma Linda University and NASA Space Radiation Element, HRP

1. ***Part 1. The space radiation environment.***

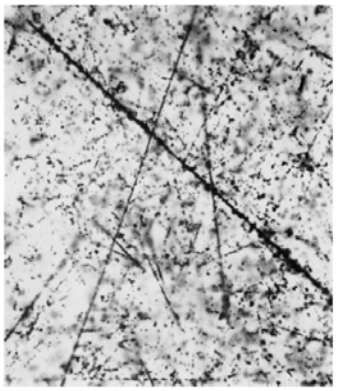


Consists of high energy charged particles originating from inside and outside the solar system which interact with magnetic fields in different regions of space to determine local composition and dose. The diagram above (NASA) illustrates Sun-Earth connection with constant emission of solar wind punctuated by large emissions of protons (and other ions) in the form of solar flares and coronal mass ejections. Geomagnetic field acts to shield near-Earth space.

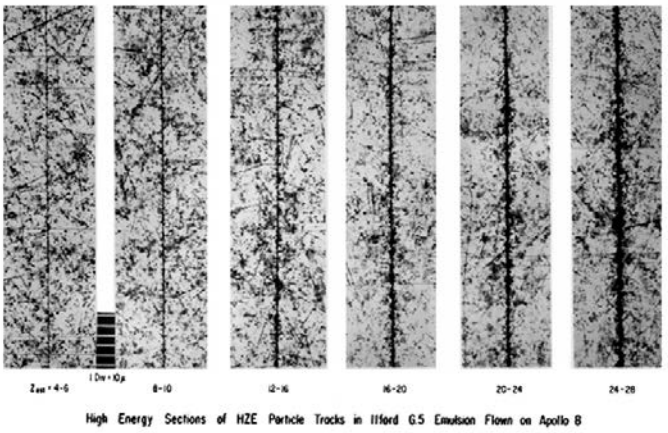
2. ***Galactic cosmic rays*** pose the greatest constant threat and are comprised of fully ionized atomic nuclei of elements from Hydrogen (Atomic number and charge number 1) to Iron (Atomic number and charge number 26). The dose from charged particles is proportional to their charge squared and is reduced by shielding. The diagram indicates the contributions of fluence (number of particles passing through a unit area), dose (energy absorbed per unit mass) and dose equivalent (dose x correction factor for human health effects) behind ~ 1.8 cm aluminum shielding as a function of element. Reference Durante, M., Cucinotta, F.A., 2008. Nature Reviews Cancer 8, 465-472.



3. ***A visual example of the space radiation field*** is shown in a nuclear emulsion (high density photographic film) worn by Neil Armstrong during Apollo 11. Ref. Schaefer & Sullivan, Radiat Res 1972; 49:245–71. Trajectories (tracks) of cosmic rays reduce silver bromide grains as they pass. Thin tracks are from protons while thick tracks are from elements of higher atomic number.



4. ***The intensity of ionization in tracks*** is proportional to their charge squared as seen in cosmic ray tracks from Apollo 8. Cosmic Ray Tracks from Apollo 8, Schaefer & Sullivan, 1972. A dense inner region or "core" is surrounded by a "penumbra" of scattered electrons (δ-rays).



5. ***Other charged particle properties.***

- Unlike X-rays and gamma rays which are absorbed exponentially with thickness of material, charged particles follow the Bethe-Bloch relation in terms of energy loss to give a "Bragg curve" which shows that they penetrate significant thicknesses before abruptly stopping as their velocity drops to zero.

- Charged particles can undergo nuclear reactions to produce showers of secondary particles.

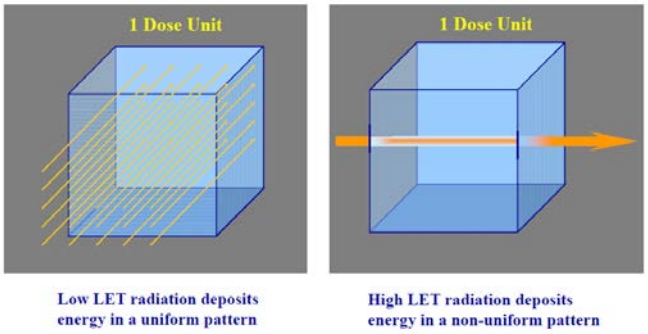
6. ***Parameters used to describe charged particle radiation.***

1) Dose (energy absorbed per mass)	How Much	Gray, mGy
2) Kinetic Energy/nucleon	How Energetic	MeV/n (compare at same velocity)
3) Fluence (# particles per area)	How Many	#/cm^2
4) Linear Energy Transfer (LET)	How Intense	keV/μm (energy loss per unit track length)

Abbreviations: GCR (galactic cosmic rays), HZE (High charge [Z] Energetic particle, RBE (relative biological effectiveness)

7. ***Dose is an inadequate description of exposure for charged particles.***

Dose is defined as energy absorbed per unit mass *(irrespective of the spatial distribution of the absorbed energy)* and fails to address track structure. Figure, G Nelson.

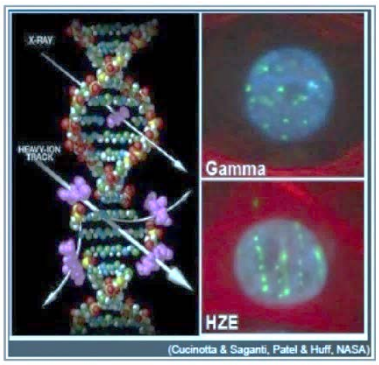


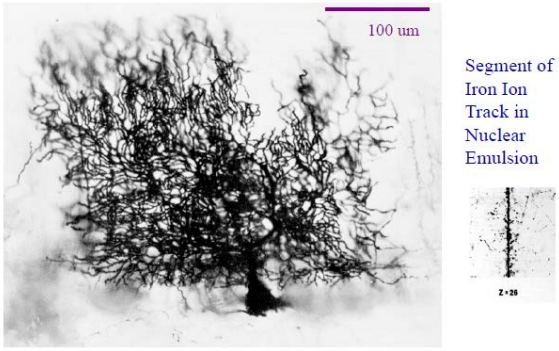
Low LET radiation such as x-rays and gamma rays deposit energy uniformly whereas charged particle deposit energy in a concentrated track. So even at equal dose, the energy deposition is dramatically different on small scales such as cells or DNA.

8. ***Track structure is dependent on many factors*** including charge, mass, velocity and interaction medium. Thus LET alone does not predict track structure. Examples of 0.45 MeV/n hydrogen, 10 MeV/n carbon, 90 MeV/n silicon and 1000 MeV/n iron ions all having the same LET of 150 keV/μm generate vastly different tracks. See ref. Plante and Cucinotta New Journal of Physics 10 (2008) 125020.

9. ***Spatially correlated damage*** may result from the passage of a charged particle through DNA, cells, or groups of cells in a tissue leading to clustered damage at different biological scales that is not observed for low LET radiation.

The figure at left illustrates DNA damage and the resulting DNA damage repair complexes assembling in cell nuclei as visualized by modified histone γ-H2AX. The figure at right illustrates a cerebellar Purkinje cell on the same scale as a track segment from an iron ion. Many dendrites or neurons in a tissue region would be simultaneously affected by such a track leading to unique biological responses.





10. ***What are the important targets in neural tissue?*** Cell nuclei? Cell soma? Axons and dendrites? Dendritic spines and synapses? Mathematical modeling by Cucinotta et al. have shown that low fluences of charged particles result in very high doses in small processes such as dendritic spines even when macroscopic dose is low. Reference: Alp et al. PLOS Computational Biology | DOI:10.1371/journal.pcbi.1004428

11. ***Space radiation doses are mission specific and scale with duration.*** Dose estimates for various current conceptual missions have been made by NASA. Estimates are sensitive to shielding estimates.

• Destination and duration • Vehicle and habitat design • Solar conditions

International Space Station
–2013-2024: 6-person crews for 6 months; 2-person crews for 12 months
–Dose limits reached after 1-3 missions

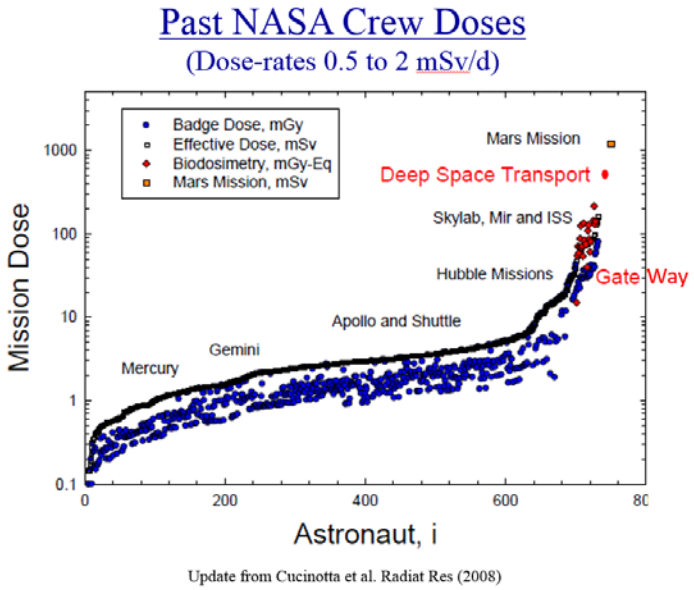
Gate Way Missions –20 –40 days in deep space
–Doses on order of 35-70 mSv–solar min; SPE protection provided
–Previous experience may limit crew selection

Deep Space Transport: (cis-lunar; 200 (EM7) –400 (EM9) day missions.)
–Outside Earth's magnetosphere in free space; no planetary protection; GCR risks major concern
–Limited number of crew will certify for EM7 & EM9 flight –depends mainly on time in solar cycle

Planetary: Mars
– 2030 and beyond: 6-person crews, up to 3 yrs.
– Long deep space transit times; mixed field environment on Mars
– 245 – 360 mGy / 1050 – 1200 mSv
– 3 to 4 times over current Permissible Exposure Limits

Deep Space Dose Rate
– 0.445 mGy/day (with appropriate shielding assumptions)
– 1.8 mSv/day measured on MSL

12. ***Past exposure levels to U.S. astronauts*** scale with mission duration and vehicle altitude.



The unit Sv (Sievert) is the absorbed dose multiplied by a unitless "Quality Factor" to reflect greater biological effectiveness of high LET particles averaged over many biological outcomes. This is called the dose equivalent. Dose equivalent rates have typically been 0.5 to 2 mSv/d.

13. ***Exposures: Mnemonic rules of thumb***

A mammalian cell nucleus is traversed by a particle on average:

Protons:	Once every 3 days
Helium:	Once every 3 weeks
Z > 2 ion:	Once every 3 months

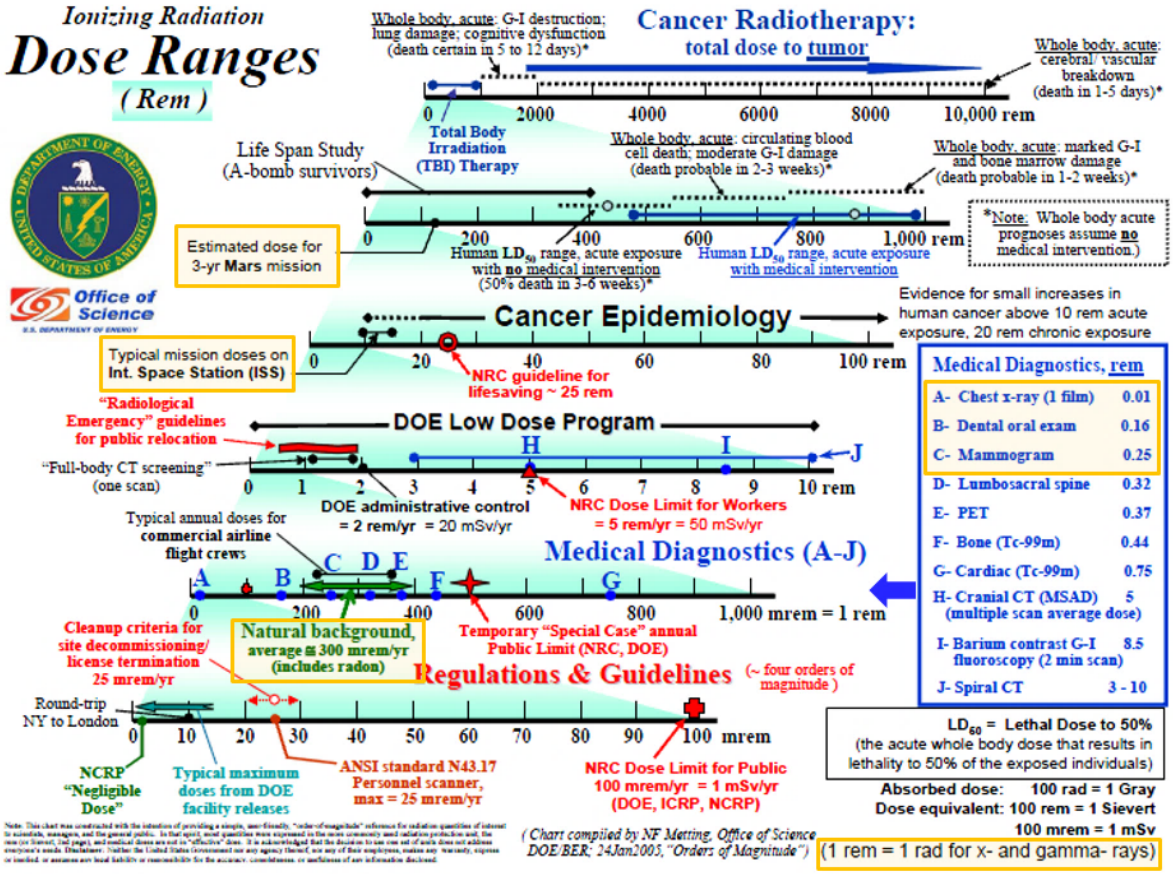
Contributions of ion groups to Mars mission exposure: ≈ 200:100:50:50:50 mGy

Protons	≈ 200 mGy
Helium	≈ 100 mGy
Z = 3 to 9	≈ 50 mGy
Z > 9	≈ 50 mGy
Neutrons	≈ 50 mGy

Total exposures: 0.445 mGy/day or 1.8 mSv/day

Reference: Nelson, G. A. Radiat. Res. 185, 349–358 (2016).

14. *Context of human radiation exposures*. A dose range summary over 6 orders of magnitude was prepared by Noelle Metting, ScD of the DOE Office of Science in 2005 and helps put space exposures into more familiar contexts. Areas highlighted in gold are modifications.



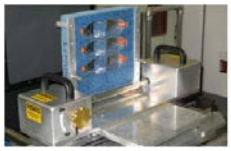
15. *NASA Permissible Exposure Limits*

To manage health risks to astronauts, NASA has established a series of guideline associated with different health outcomes. These are found in NASA-STD-3001, Volume 1. Limits for lens, circulatory system, and central nervous system are imposed to limit or prevent risks of degenerative tissue diseases. Current Permissible Exposure Limits (PELs) are shown below.

Organ	*30 day limit*	*1 Year Limit*	*Career*
Lens*	1000 mGy-Eq	2000 mGy-Eq	4000 mGy-Eq
Skin	1500	3000	4000
BFO	250	500	Not applicable
Heart**	250	500	1000
CNS***	500	1000	1500
CNS*** (Z≥10)	-	100 mGy	250 mGy

*** for CNS indicates that limits are estimated for hippocampus as reference location. These have not been updated in light of more recent data.

16. ***Ground based studies of charged particle*** "space-like" radiation are conducted at particle accelerators. NASA and the Department of Energy established the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), Upton, NY for biology and physics experiments with charged particles of space like energies and doses. The NSRL is part of the BNL accelerator complex and functions together with biological laboratories at the BNL Biomedical Department. The NSRL has dedicated animal and cell biology facilities co-located with a research beamline designed with mounting fixtures for biological samples.



The NASA Space Radiation Laboratory can provide selected particles from hydrogen to gold at energies up to 1.5 GeV/n in fields up to 60 x 60 cm. Full dosimetric characteristics of experiments is provided to facility users. New technical advances are enabling multi-ion exposures to better simulate the real space radiation environment or the environment inside the human body while on a deep space mission ("Local Field" galactic cosmic ray simulation model)..

17. ***Biological reasons to use multi-ion simulation.***

- Dose responses are not all linear
  - e.g. U-Shaped
- Particle effects may be unique
  - Effects may trend oppositely
  - Quality factors very hard to define
- Mixed particle exposures may not produce simple additive responses
- Sequential exposures don't always produce simple additive responses
- The "algebra" for combining different ions and in what sequence is poorly understood in terms of whether outcome measures would exhibit additive, super-additive or antagonistic responses.
- Dose rate effects unclear for particles
  - What are the biological time constants?

18. ***Part 2. Effects of Space-like radiation on the central nervous system (CNS)***

19. ***Radiation Responses of CNS***

Traditionally, based on time of expression, radiation-induced CNS injury has been divided into three reactions: Acute, Early Delayed and Late Delayed. These are summarized in the table below.

STAGE	TIMELINE	PATHOLOGY	SYMPTOMS	MECHANISMS	PROGNOSIS
Acute	Days and weeks	Inflammation	Encephalopathy: headache, nausea, vomiting	Increases of vascular permeability	Reversible Spontaneous resolution
Early Delayed	1 to 6 months	Transient demyelination	Somnolence	Loss of oligodendrocytes	Reversible Spontaneous resolution
Late Delayed	More than 6 months	Demyelination, vascular damage and white matter necrosis	Increased morbidity and mortality	Multitarget	Irreversible and progressive

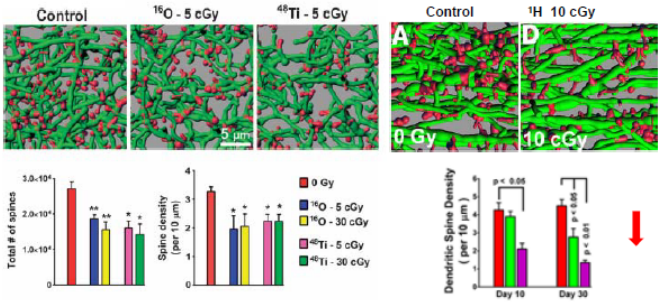
This classification scheme is based on clinical experience with radiotherapy for which exposures are typically multiple daily fractions of 2 Gy totaling 40 to 60 (or more) Gray and delivered to small targeted volumes. Most of these effects are observable only after large doses and are not significant in the low dose range below a few Gray (as in space). What happens in the low dose regime after exposure to charged particles?

20. ***Observations from astronauts*** in space have shown that the passage of single particles through elements of the visual system can produce "light flash" illusions indicating that they evoke responses that rise to the level of conscious perception. Single particle traversals represent the minimum exposure for charged particles. References: L Narici. New Journal of Physics 10 (2008) 075010 and W.G. Sannita et al. Vision Research 46 (2006) 2159–2165.

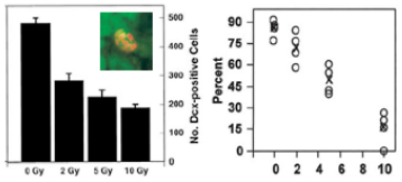
21. ***NASA has developed a set of 8 gap questions*** to address the CNS health risks from radiation exposure. These are listed in Appendix B.1

22. *CNS radiation risk supporting evidence.* Neurogenesis and neuronal structure

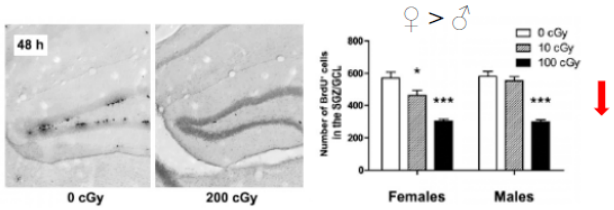
- Experimental Models
  - Neurogenesis in rodent dentate gyrus
  - Embryonic brain development
  - Dendritic arbor and spines in adult rodent
- Lowest Effective Doses
  - Neuron structure – 5 cGy HZE, 10 cGy protons
  - Neurogenesis in mouse DG - 10 cGy protons, 50 cGy HZE, 50 cGy gamma rays.
  - No effect of fractionation over 5 days.
- RBE's
  - 2-4 rodent DG
  - 1-4 – 9.8 rat & fish embryos
  - 3.4 cultured human NT2cells
  - Rat spinal cord myelopathy at high dose.
  - C vs X-ray 1.37 – 2.16



Mouse. Dendritic Spine # and Density. ^{16}O and ^{48}Ti ions. 8 weeks post IR.
Mouse. Spine Density. Protons. 30 days post IR.



Mouse. X-rays. Total BrdU+ cells and % BrdU+ developing neurons
48 hours & 2 months post IR.



Mouse. Total BrdU+ Cells. Protons. 48 hours post IR.

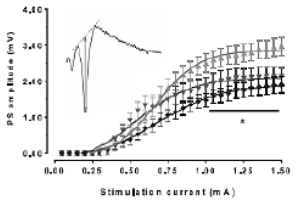
Upper right. Neuronal GFP expression and confocal microscopy used to score dendrite branching and spines. Decrease indicates fewer synapses and less connectivity which impairs information processing. Such spine and dendrite reductions are seen in neurodegenerative diseases. Parihar et al. Sci. Adv. 2015;1:e1400256 1 May 2015, Parihar et al (2015) Brain Structure and Function 220: 1161-1171.

Lower Left. BrdU labels mouse dividing neuronal precursor cells (pluripotent). Double staining with NeuN and BrdU labels newly born immature neurons. The newly born cells are incorporated into neural networks and defects in neurogenesis correlated with memory impairment. Mizumatsu et al. Cancer Research 63, 4021–4027, July 15, 2003

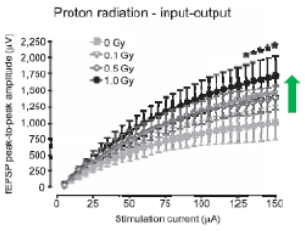
Lower Right. Total neuronal stem cells staining for BrdU. Note sex difference. Sweet et al. Radiat. Res. 182, 18–34 (2014). Other supporting data: Debus et al Radiat. Res. 160, 536–542 (2003).

23. *CNS Radiation Risk Supporting Evidence.* Neuronal Function

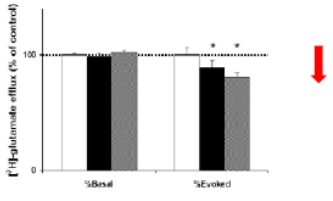
- Experimental Models
  - Extracellular (field) recordings in mouse and rat hippocampal slices
  - Patch clamp (single cell) recordings in mouse hippocampal slices
  - Stimulated release of neurotransmitter from synaptosomes – 20 cGy HZE
- Lowest Effective Doses
  - Synaptic excitability in DG - 100 cGy protons.
  - Synaptic plasticity & LTP n CA1 – 10 cGy Fe & 25 cGy Si
  - Synaptic transmission in DG – 100 cGy protons.
  - Intrinsic neuron properties - 100 cGy protons.
  - Synaptosome transmitter release – 20 cGy
- RBE's
  - Evidence for < 1 and ~ 20, & U-shaped D-R. Ions may elicit opposing trends



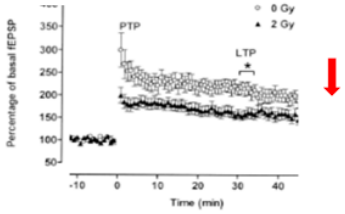
Mouse. Synaptic excitability of CA1 pyramidal cells. ^{28}Si ions. 3 months post IR



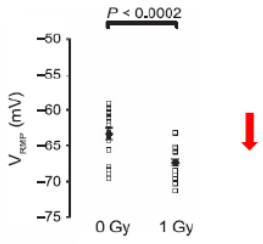
Mouse. Synaptic excitability of DG granule cells. Protons. 3 months post IR



Rat. Hippocampus synaptosomes. Stimulated glutamate release. 60 cGy ^{56}Fe ions. 3 & 6 months post IR



Mouse hippocampus Long Term Potentiation of CA1 cells. ^{56}Fe ions. 3 months post IR.



Mouse hippocampus. Resting membrane potential of CA1 pyramidal cells. Protons. 3 months post IR

Upper Right. Field recordings in CA1 (left) Rudobeck et al. Radiat. Res. 181, 407–415 (2014) and dentate gyrus (right) Marty et al Radiat. Res. 182, 653–665 (2014) showing impaired excitatory response in CA1 pyramidal cells but enhanced excitability in DG granule cells (possibly due to impairment of inhibitory activity leading to more excitation).

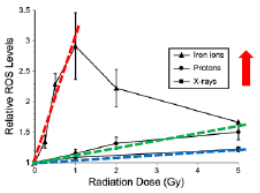
Lower Left. Hypertonic shock stimulated release of neurotransmitter from purified synapse bearing microsomes (synaptosomes) was impaired indicating presynaptic neurotransmitter vesicle fusion defect. Machida et al. Radiat. Res. 174, 618–623 (2010). Other supporting data Britten et al Radiat. Res. 182, 292– 298 (2014).

Lower Middle. Repeated stimulation of CA3 cell axons causes long term potentiation of receiving CA1 pyramidal cells indicating sysnaptic strengthening in a tissue level model of memory trace formation. Radiation impaired synaptic plasticity. Vlkolinsky et al. (2007) Effect of ^{56}Fe-particle radiation on synaptic plasticity.

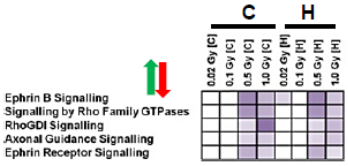
Lower right. Patch clamp recordings from individual CA1 pyramidal cells indicates that cell resting membrane potential was increased (in the negative direction). The further hyperpolarized cells are more difficult to depolarize and hence less easy to stimulate into firing action potentials. Sokolova et al. Radiat. Res. 183, 208–218 (2015).

24. *CNS Radiation Risk Supporting Evidence:* Inflammation, Microenvironment and Disease

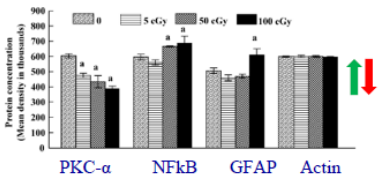
- Experimental Models
  - Inflammatory Markers & Cytokines
  - Microgliosis and Astrogliosis
  - Proteotoxicity
  - Gene Expression
  - Vasculature Changes
- Lowest Effective Doses
  - Inflammatory Markers – 5 cGy HZE, 10 cGy protons & adaptive effect
  - Microgliosis and Astrogliosis – 100 cGy HZE
  - Tg Mice Aβ deposition – 10 cGy HZE
  - Gene Expression – 2 cGy gamma, 50 cGy HZE
  - Vascular remodeling & BBB breakdown – 50cGy
- RBE's
  - Gene expression: Qualitatively different patterns
  - Fe & H vs γ for ROS initial slope – 47 and 2.7.
  - Petechial hemorrhages – 1.4 – 2.1 Ne/Fe vs X-ray



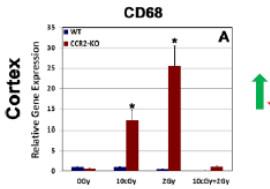
Mouse. Neural precursor cells – ROS levels X-rays, protons, ^{56}Fe ions. 6 hrs post IR.



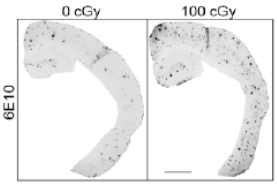
Mouse neonates. Cytoskeleton-related gene expression in Cortex [C] and hippocampus [H]. ^{60}Co gamma rays. 7 months post IR.

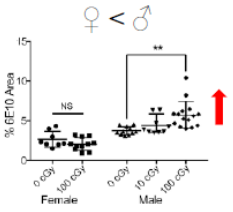


Rats. Inflammatory markers – Western Blots. ^{16}O ions. 36 hrs post IR.



Mouse. Cortex Microglia Activation. γ-rays, adaptive effect. 30 days post IR.





Mouse (APP/PS1 Tg). Amyloid deposition, cortex. ^{56}Fe ions. 6 mo post IR.

Upper left. Initial production of reactive oxygen species measured by redox sensitive dye in cultured mouse neuronal precursor cells organized as neurospheres. Limoli et al. Radiat Environ Biophys (2007) 46:167–172.

Upper right. Measurements of gene expression patterns (mRNA) from mouse hippocampus. Panel shown is genes involved in cytoskeleton of dendrites and spines. Kempf et al. Molecular Neurodegeneration 2014, 9:57

Lower Left. Western blots of inflammatory markers: protein kinase C (signal transduction target of inflammatory cytokines), NFkB (key oxidative stress transcription factor), GFAP (astrocyte activation marker) and B-actin (loading control). Poulose et al. Radiat. Res. 176, 761–769 (2011).

Lower middle. Microglia activation marker after Cesium gamma rays delivered as small priming dose and large challenge dose 24 hrs later. Demonstrates protective adaptive effect and illustrates significance of small dose. Microglia are resident immune cells and maintain synaptic integrity. Acharya et al. PLoS ONE | DOI:10.1371/journal.pone.0128316 June 4, 2015 1.

Lower right. Staining of amyloid plaques in transgenic mouse cortex with Abeta antibody 6E10 indicating sex-specific differences in radiation-stimulated plaque formation (accelerated onset of Alzheimer-like pathology). Cherry et al. PLoS ONE 7(12): e53275. doi:10.1371/journal.pone.0053275.

25. ***Inflammation, microenvironment and disease***. Other examples.

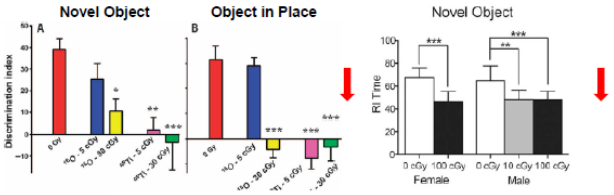
- Oxidative stress-mediating transcription factor NF-κb is induced by low dose ^{16}O ions in rat hippocampus. NF-κB induction at 36 hrs with 0, 50, 100 cGy. Poulose, et al. Radiat. Res. 176, 761–769 (2011).
- Similarity of low dose irradiated mouse vs aging human gene expression patterns. 10 cGy gamma rays. Mouse Brain vs Normal Aging Human Brain. Lowe & Wyrobek.
- Sequential irradiation with protons and iron ions induces non-additive response for neuro-inflammatory cytokines MDC, Eotaxin and IL-6 at 3 months post irradiation. Raber, Allen, Rosi, Fike.
- Peripheral monocytes infiltrate brain after irradiation and acquire an activated microglia phenotype. Morganti et al. PLoS ONE (2014) 9(4): e93650.
- Endothelial cell densities after proton and iron irradiation. Mouse hippocampal microvessel length density exhibits 20% loss (H) or 34% loss (Fe) at 12 months after irradiation with later recovery. X Mao.

26. ***Many behavioral measures*** have examined charged particle effects in the 0.01 to 1 Gy range.

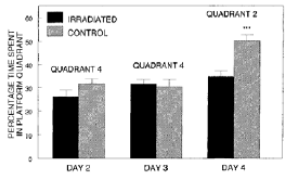
- Wire hang, rotarod and accelerod coordination.
- Conditioned taste aversion.
- Operant responding
- Acoustic startle
- Open field
- Novel Object, Place and Temporal Order
- Morris water maze
- Barnes maze / Pattern Separation
- Elevated plus & zero mazes
- Attentional set shift
- Psychomotor vigilance
- Contextual and Cued Fear conditioning
- Emesis
- (Emerging data on social interactions)

27. *CNS radiation risk supporting evidence behavior:* Memory & motor coordination.

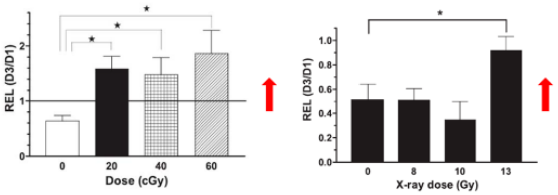
- Experimental Models
  - Novel object and object in place recognition in mouse and rat
  - Maze performance in mouse and rat
  - Fear conditioning mouse and rat
- Lowest Effective Doses
  - Novel object & place, mouse – 5 cGy HZE
  - Barnes maze, rat – 20 cGy HZE
  - Operant responding - 20 – 50 cGy Si & Ti, 50 cGy Fe
- RBE's
  - Rat Barnes Maze ~50
  - Photons effective but minimum dose not established



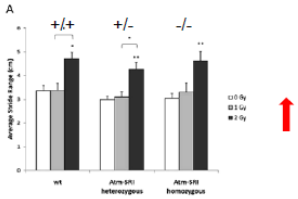
Mouse. NOR & OiP. ^{16}O and ^{48}Ti ions. 8 weeks post IR.
^{56}Fe, APP/PS1 Tg Mouse. 6 weeks post IR.



Rat. Water Maze. ^{56}Fe 1.5 Gy whole body. 1 month post IR.



Rat. Barnes Maze. ^{56}Fe vs 125 kV X-rays, head-only. 3 months post IR.



Mouse ± ATM DNA Checkpoint & Repair Gene. Gait Variability. ^{56}Fe 0 - 2 Gy whole body. 6 months post IR.

Upper Left. Novel object recognition (replace old object with new and measure relative time exploring new object) or Object in place (move one object to new location) and measure relative time with object at new position. Integrates spatial memory and associations. Parihar et al. Sci. Adv. 2015;1:e1400256.

Upper right. Novel object recognition w. sex differences. Cherry et al PLoS ONE 7(12): e53275.

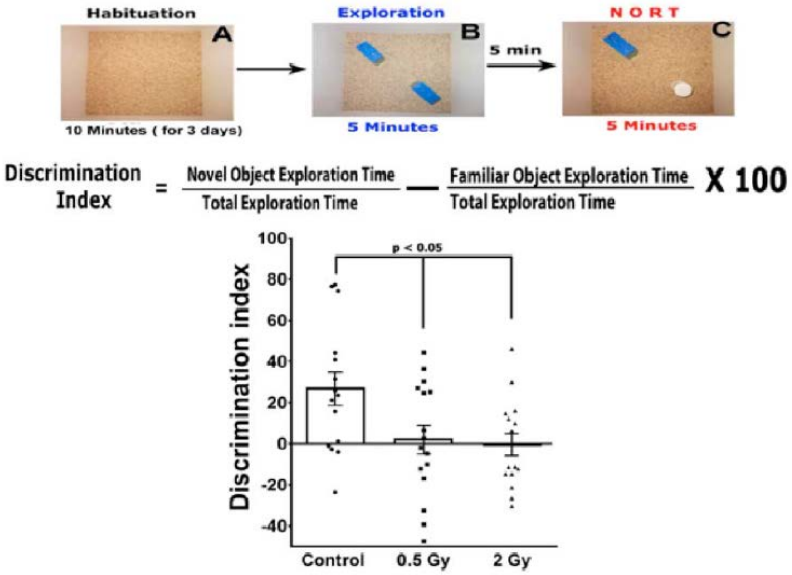
Middle . Morris water maze. Rat trained to position of hidden platform then move platform to quadrant two and rat with good memory continues to look in quadrant 4. Impaired rat uses more random search strategy. Measure % time at quadrant 4. Shukitt-Hale et al. Radiat. Res. 154, 28–33 (2000).

Lower Left. Animal placed on a Barnes maze consisting of a large circular platform with holes at periphery. One leads to an escape box below. Visual cues in surrounding room. Measure time it takes to find escape box on day 3 vs day 1. Measure of spatial memory. Note huge dose differences between iron ions and x-rays. Britten et al. Radiat. Res. 177, 146–151 (2012).

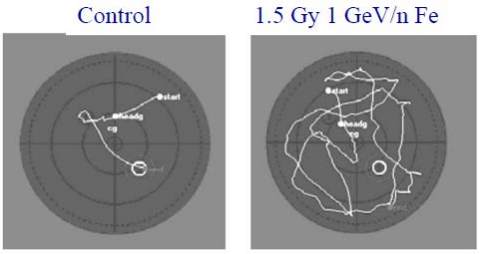
Lower right. Motor coordination assessment by gait consistency; animals were trained to walk through a narrow alley leading into their home cage leaving ink footprints on paper. The ATM gene status acutely important in managing DNA damage had little or no influence on the outcome. Yamamoto et al. Radiat. Res. 175, 231–239 (2011). Supporting data. Melville et al. (1966). Kim et al. J Rad Res 49: 517 (2008)

28. ***Memory.*** Additional examples from animal models.

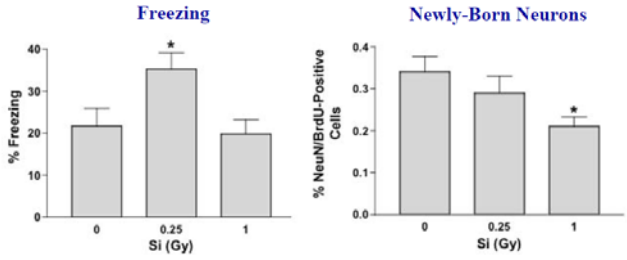
- Inhibition of Novel Object Recognition at 1 mo after 0.5 and 2 Gy Proton Irradiation. Proton irradiation impairs novel object recognition (NOR). Similar results observed for novel place recognition. Limoli et al.



- Morris water maze. Hippocampal dependent spatial memory. B. Rabin et al.

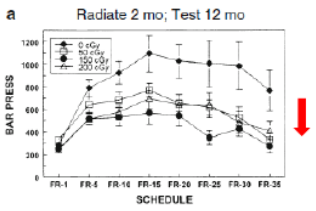


- Hippocampus-dependent contextual freezing and Dentate neurogenesis. 3 months after exposure to silicon ions freezing behavior and neurogenesis are altered in the same animal with a complex correlation. J Raber et al.

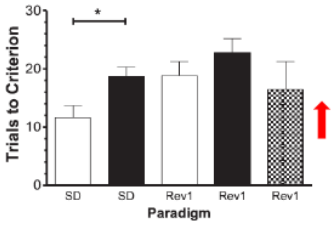


29. ***CNS radiation risk supporting evidence behavior***: Executive function.

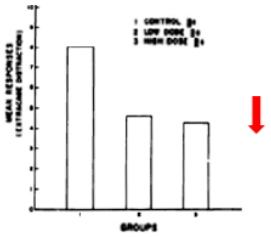
- Experimental Models
  - Operant Conditioning
  - Attentional Set Shift
  - Psychomotor vigilance
  - Conditioned Taste Aversion
  - Non-human Primate data
- Lowest Effective Doses
  - Operant Conditioning – 25 cGy ^{56}Fe, 1 – 25 ^{16}O
  - Attentional Set Shift – 10 cGy – 25 cGy HZE
  - Psychomotor vigilance - ≥ 20 cGy protons
  - Non-human Primate data ~ 80 cGy
  - CTA - 10 – 25 cGy, Si & Ti; 50 cGy Fe
- RBE's
  - CTA ~ 10 for Fe vs γ at ED_{50}



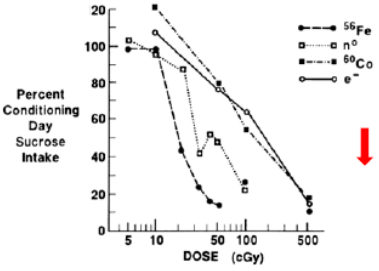
Rat. Operant Conditioning. ^{56}Fe ions – 0, 50, 150, 200 cGy. 10 months post IR.



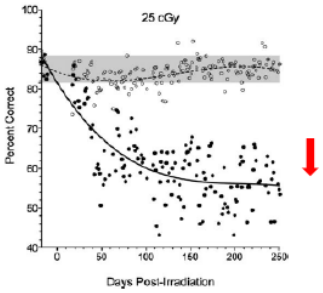
Rat. Attentional Set Shift Tests. ^{56}Fe ions – 0, 15, 20 cGy. 3 months post IR.



Rhesus Monkey. Responses to Extraneous Distraction. Mixed γ + neutron 76 to 609 cGy . 14 months post IR.



Rat. Conditioned Taste Aversion. 4 Radiations. 30 – 250 days post IR.



Rat. Psychomotor Vigilance. Protons. 30 – 250 days post IR.

Upper left. Fewer bar presses per food pellet reinforcement indicating impairment of reward-based conditioning. Rabin et al. AGE (2012)

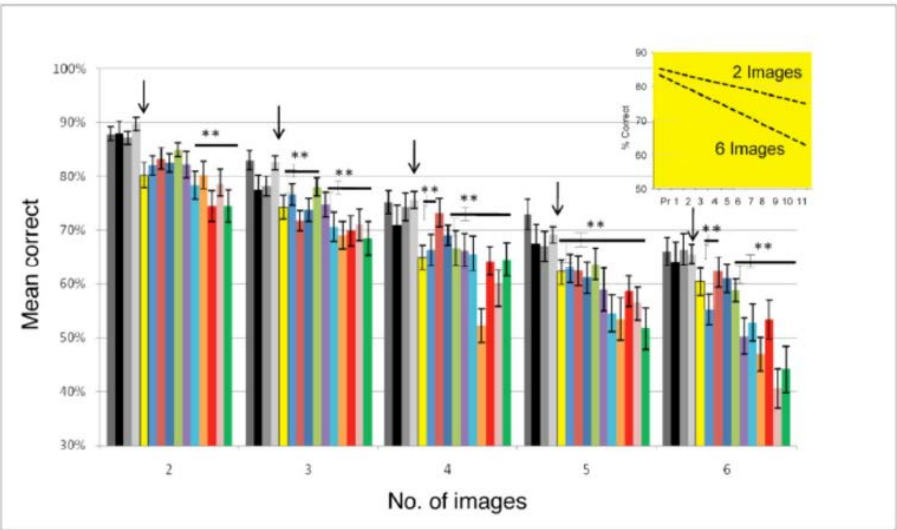
Upper right. Animal taught to associate flavored food reward with a scented sterile sand cue and dig to receive reward. Then food flavor and scent cue combinations manipulated to force unlearning of first pattern with replacement by new pattern. SD and Rev1 refer to original and new (reversal) trials. Complex tasks requiring executive function associated with frontal cortex. Britten et al. Radiat. Res. 182, 292–298 (2014).

Lower left. Male monkeys performing an object manipulation task were less distracted by the presence of a female introduced into the same room. Indicates less distractability or poorer overall attention. Melville et al. (1966)

*Lower middle***.** Norway rat sucrose intake after taste aversion training. Bevalac iron ions, AFFRI neutrons, cobalt and LINAC electrons. B Rabin, W Hunt, & J Joseph. Rad Res. 119: 113-122 (1989)

Lower right. Examples of performance accuracy for rats trained to push lighted button for food reward. Timing interval critical for reward and animals must be attentive to light on signal and not push button without cue. Reaction time and attention to task assessed. The percent correct scores are shown as a function of days post-exposure, with each dot representing a separate session. Data points to the far left on each graph indicate baseline performances prior to exposure. Shaded areas indicate the range of a 95% confidence interval around the pre-exposure baseline performances of all nonexposed control animals. Closed circles: Animals identified by cluster analysis as being radiation-sensitive; open circles: Average performances of all unexposed control animals. Davis et al. Radiat. Res. 181, 258–271 (2014).

30. ***Cognitive function in Rhesus monkeys*** after fractionated therapy doses to head (25 Gy total). Delayed match to sample tests with different levels of complexity.



Fractionated whole-brain irradiation leads to chronic, progressive cognitive impairment. Each bar represents the mean percentage (±SEM) of correct trials, with two to six images summed over all animals, trials, and daily sessions for each month. Arrows indicate the start of irradiation. **P < 0.001; horizontal bars span months where asterisks apply. The inset shows a regression analysis of the average monthly performance of the three NHPs at low (two images) and high (six images) cognitive load. Reproduced from Figure 2 of Robbins et al. (2015).

31. ***CNS Radiation Risk Supporting Evidence:*** Human Adult Exposures

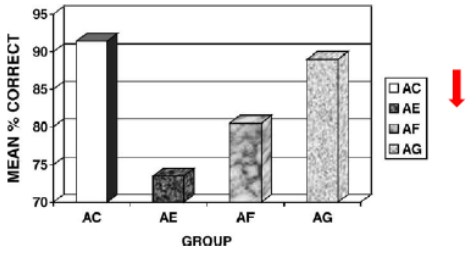
- Exposure Scenarios
  - Chernobyl
- Lowest Effective Doses
  - Cognitive Testing, Chernobyl ~ 13 cGy
  - EEG – several Gy
  - Schizophrenia Incidence. ~ 30 cSv.
  - Misc. Neuropsych. Parameters > 15 cSv
- RBE's
  - No high LET data

In adults, "radiation associated cerebrovascular effects" were obtained at > 15 cSv – 25 cSv. Dose-related "neuropsychiatric, neurophysiological, neuropsychological, and neuroimaging abnormalities" following exposure to > 30 cSv. *Loganovksy 2009 Chernobyl Review.*

Human. Misc. Neuropsychological Measures. Chernobyl. 15 cSv. ≥ 4 years post IR

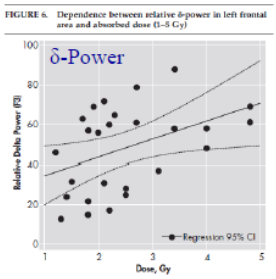
Significant increase in the "incidence of schizophrenia in EZ personnel" in comparison to the general population (5.4 per 10,000 in the EZ versus 1.1 per 10,000 in the Ukraine in 1990). Those irradiated by moderate to high doses (> 30 cSv), including ARS patients, had significantly more "left frontotemporal limbic and schizophreniform syndromes". *Loganovksy & Loganovskaja 2010 Chernobyl Review*

Human. Schizophrenia Incidence. Chernobyl. 30 cGy. ~ 4 years post IR



Avg. Doses : AC= 0 AE=63 AF= 12.6 AG= 8.8 cGy

Human. Code substitution-immediate recall (CDI). Chernobyl. ~10 years post IR.



Dose dependence
p< 0.05 by ANOVA

Human. EEG. Chernobyl. 1 – 5 Gy. ~ 10 years post IR. (p < 0.05 for ANOVA dose dependence)

Upper right. A cognitive test battery was given to people living and working near Chernobyl. AC = controls. AE = expeditors who cleaned up the site. AF = forestry workers living nearby. AG = agricultural workers living further away. Gamache Archives of Clinical Neuropsychology 20 (2005) 81–93

Lower text and panel. Summary of findings from Chernobly MD review where definitions of individual measures were vague. EEG vs dose plot showing power analysis of rhythms in a particular frequency range indicative of cortical electrical activity. Loganovsky Data Science Journal, 23 June 2009; Loganovsky and T. Loganovskaja. Schizophrenia Bulletin, Vol. 26, No. 4, 2000.

32. *CNS Radiation Risk Supporting Evidence:* Human Pediatric Exposures

- Exposure Scenarios
  - A-Bomb & Chernobyl
  - Tinea capitis
  - Scalp hemangioma
  - Childhood radiotherapy
- Lowest Effective Doses
  - Fetal exposure cognitive impairment – 1 – 20 cGy
  - Scalp hemangioma cognitive impairment– 25 cGy
  - Tinea capitis cognitive impairment & social success measures – 1.3 Gy
  - Cog. impairment scales with dose for Rx 18 – 36 Gy
- RBE's - No high LET data

Dose to brain (mGy)	Crude	Adjusted*	Adjusted†
0-20	–0.10 (0.10)	–0.05 (0.11)	0.03 (0.11)
>20-100	0.07 (0.09)	0.09 (0.10)	0.10 (0.10)
>100-250	0.23 (0.11)	0.25 (0.11)	0.24 (0.11)
>250	0.35 (0.19)	0.46 (0.20)	0.42 (0.20)
β coefficient (95% CI) per 50 mGy	0.07 (0.03 to 0.11)	0.07 (0.03 to 0.11)	0.06 (0.03 to 0.10)
P for trend‡	0.0002	0.0003	0.0008

Sig.

*Adjusted for number of siblings, age at treatment, year of test, and father's occupation. †Adjusted for number of siblings, age at treatment, year of test, father's occupation, and high school attendance.

Human. Spatial recognition test. Hemangioma treatment – Low LET. ~ 16 years post IR.

Table 3. Performance and Impairment Rates on Neurocognitive and Behavioral Outcomes

Functional Outcome	Mean	SD	Range	% Impaired*	*P*†
Intelligence	0.05	0.99	−2.67-1.733	14.8	.76
Attention					
Selective	0.43	0.89	−2.47-1.67	8.2	1.00
Sustained	−0.04	1.41	−6.00-0.80	12.1	**.004**
Variability	−0.42	1.19	−3.70-1.70	29.3	**.01**
Span	−0.18	0.91	−1.86-1.81	27.9	**.01**
Memory					
New learning	−0.27	1.04	−2.00-1.60	29.5	**.03**
Short-term recall	−0.41	0.97	−3.00-1.50	45.9	**.001**
Long-term recall	−0.30	0.93	−2.00-1.50	34.4	**.006**
Executive function					
Cognitive flexibility	0.09	1.02	−3.80-1.47	14.8	.96
Cognitive fluency	−0.32	0.91	−2.67-1.33	24.6	**.007**
Working memory	−0.25	0.73	−1.97-1.56	13.1	**.03**
Fatigue	35.58	11.39	8.00-60.00	29.0	**< .001**

*Impairment defined as scores falling at least one standard deviation (SD) below the expected mean. *P* values based on one-sample *t* test of mean performance referenced to expected mean of 0 and SD of 1.
†*P* values ≤ .05 identified in **bold** and correspond to functional outcomes used in subsequent analyses with brain imaging and cardiopulmonary functions.

Human. Cognitive Impairment. > 30 Gy Thorax Dose X-rays for Childhood Hodgkins Lymphoma . Adult Testing.

Fetal Exposures. Chernobyl. Dose related *cognitive impairment*. Gestation ages of 8 weeks: threshold >20 mSv. At 16–25 weeks: neuro-psychological abnormality thresholds were >10 mSv and >200 mSv, respectively.
A-bomb. Fetal exposures led to ***mental retardation***. Thresholds of 6-31 cGy for 8 – 15 week gestational ages and 28 – 37 cGy for 16 – 25 week gestational ages.

Loganovsky 2009 Chernobyl Review.
Otake 1996 A-bomb Review

Upper right. Summary of cognitive tests administered to adults who had been exposed to whole thorax dose in treating Hodgkins lymphoma. % Impairment indicated. Krull et al. J Clin Oncol 30:3618-3624. Hall et al. BMJ 2004;328;19- doi:10.1136/bmj.328.7430.19, Armstrong et al. JNCI Vol. 101, Issue 13 | July 1

*Lower Left***.** Results of cognitive testing during military enrollment at age 18 in Swedish men treated for scalp birthmark as young children. Increase in parameter indicates poorer performance. Hall et al. BMJ 2004;328;19- doi:10.1136/bmj.328.7430.19

Lower right. Text summary of fetal exposure resulting in later cognitive impairment. Loganovsky Data Science Journal, 23 June 2009; E Ron et al. (1982) Am J Epidemiol 116: 149 – 160. Tinea capitis.

33. ***Cognitive effects of human low dose radiation exposures, summary [Excludes medical treatments]***

- Children exposed in the 1950's and 60's to cranial doses for *Tinea capitis* and hemangioma treatments exhibited cognitive decline and more frequent psychiatric problems as young adults
- Atomic bomb survivors exposed at age >= 13 have shown no obvious cognitive decline to date (correcting for normal Alzheimer and stroke incidence)
- Chernobyl works have shown abnormal EEGs and increased incidence of schizophrenia
- Children exposed whole body for leukemia/lymphoma treatment (>= 18 Gy) show later cognitive impairment as do brain tumor patients treated locally with high doses (>50 Gy).

34. ***Summary: CNS Responses to Low Dose Ionizing Radiation***

- Minimal gross histopathological changes
- Persistent reduction of dendritic complexity and spine number
- Altered intrinsic nerve membrane properties (V_m, R_{in}, mEPSC)
- Changes in synaptic function (excitability and plasticity)
- Pre- and post-synaptic targets
- Decrements in LTP and LTD (field specific)
- Inhibitory cell type specific
- Late loss and restoration of endothelial cells and capillaries
- Persistent reduction in neurogenesis
- Lineage specific & associated with increased activated microglia
- Persistent oxidative stress, altered gene expression and low level inflammation
- Infiltration of peripheral monocytes acquiring activated microglia phenotype
- Accelerated amyloid & tau deposition, sex specific
- Disruption of a variety of behaviors related to cognitive function and memory in Hippocampus, pre-Frontal Cortex, Amygdala, Thalamus, Medulla
- Non-linear responses observable at doses in space dose range and as low as 1cGy
- Adaptive responses for cytokines
- U-shaped dose responses
- Does not scale monotonically with LET
- Anecdotal observations

35. ***Impediments to Risk Estimation***

- Valid methods for extrapolation to humans
- No accepted definitions of “significant impairment”
- Non-linear (e.g.U-shaped) dose responses *across space radiation dose domain*
- Dose, dose rate and ion species dependence
- Not monotonic with LET
- Brain region specific responses
- Physical target not well defined
- Interactions with other space flight factors

Presentation 4

Executive summary of the human-to-animal mapping matrix for high priority domains.
NASA Task NNJ17HP01P to USBRITA Consulting

Richard Britten, Ph.D
Eastern Virginia Medical School

This study was a preliminary evaluation of current animal and human behavioral models and their status/applicability for estimating human risks in the spaceflight context. It served as a point of departure to organize the workshop.

1. *Similarities and disparities between the neurocognitive/behavioral assessments made on astronauts and in ground-based rodent studies on the impact of space radiation.*

Richard A. Britten, PhD[1] & Stephen I. Deutsch MD, PhD[2] (1) Depts. of Radiation Oncology & Microbiology and Molecular Cell Biology; (2) Dept. of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School, Norfolk, Virginia. USA

2. *HFBP and SRPE Research*

Human Factors, Behavior and Performance research acquires data from humans during spaceflight and in various spaceflight analog environments. It is based on ~ 60 years of astronaut experience and focuses on fatigue, sleep, crew performance and psychological issues and development of countermeasures.

Space Radiation research uses animal models in ground-based simulations of radiation (and occasionally radiation plus simulated low gravity) environments do address the central question of whether mission relevant cosmic ray doses impact cognition and behavior.

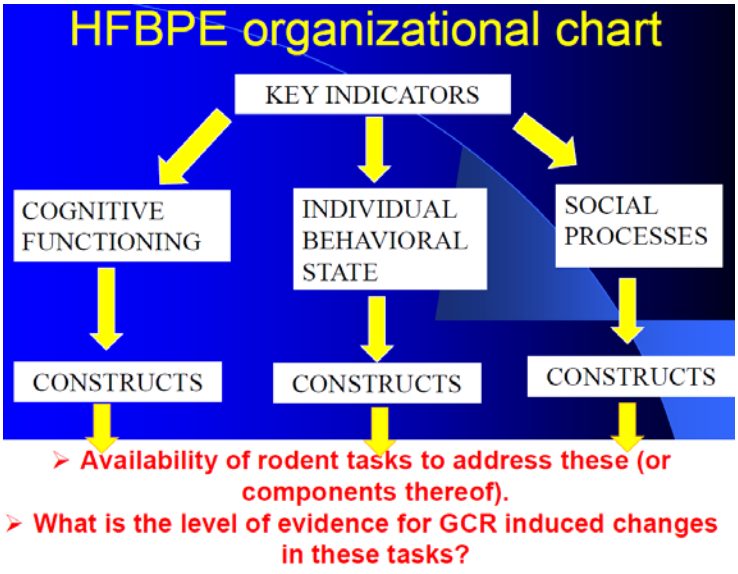
3. *How big of an issue is hadron-induced cognitive impairment?*

- Multiple cognitive domains are impaired by low GCR doses.
- Do we know enough about how GCR exposure impacts the HFBP measures?
- Do known “co-variants” for HFBP impact upon the severity of HICI?
- Mars-specific factors (e.g., crew resilience) could impact mission success. What ground analogs could be used to determine whether GCR exposure alters such factors?

4. ***Are rodents enough?***
   - Historically thought that NHP [non human primates] need to be used to study "Higher" cognitive processes.
   - Word Association, Abstraction & Emotional Identification- probably true.
   - Recent (>2008 CE) studies suggest that rats have "metacognitive" ability and advanced neural architecture (Kepecs et al, 2008; Hanks & Summerfield, 2017).
   - How many HFBP measures can be studied effectively in rodents (to assess impact of GCR exposure)?

5. ***The HFBPE and SRPE Standard Measures Table Task. Main product of task.***
   NNJ17HP01P (USBRITA Consulting)
   - Establish the HFBP behavioral measures that can be addressed in ground based rodent models.
   - Establish the level of evidence that GCR exposure impacts upon HFBP measures.
   - Identify behavioral measures that are impacted by GCR exposure and now need to be studied in more detail (HFBP co-variant effects).
   - Such studies will be large: need to prioritize what HFBP measures are most important to mission success *(NASA programmatic decision).*

6. ***HFBPE organizational chart***



7. ***Study maturity: Can we / are we / have we chart. Simplified to one table per key indicator.***

Colour Coding

Dark Green- Assays available and hadron data accrued/accruing

Light Green- Assays available and X-ray data

Yellow- Assays available, no radiation data

Orange- Data accrued but no hadron impact, or data could be accrued presently, or data may be accruing but insufficient knowledge.

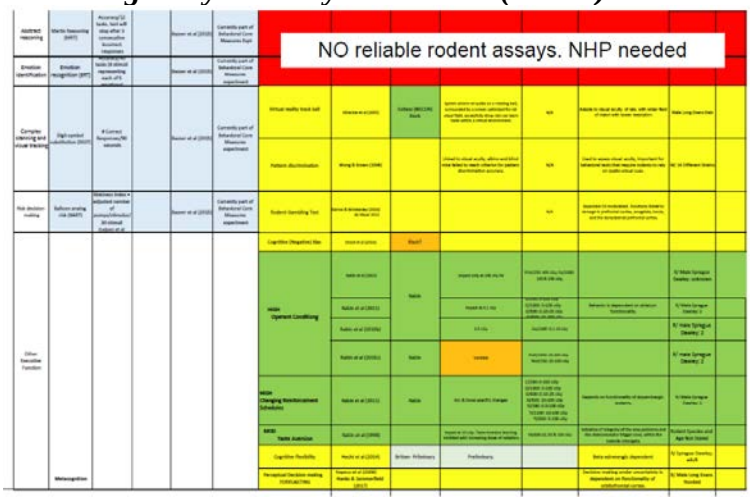
Red- No appropriate rodent based assays: NHP may be needed.

Tables have been populated with published data. Most recent data (lowest dose for some PIs). In some cases there are NASA funded individuals who are working on some areas, but have not yet published.

8. ***Cognitive functioning study maturity assessment (HIGH)***

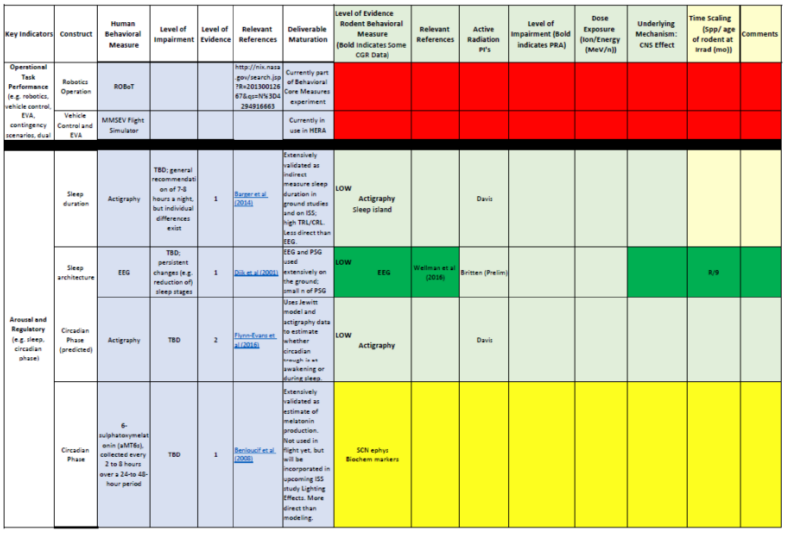
- Large number of rodent assays that encompass multiple components of HFBP behavior measure.
- Mission relevant dose (impact) data.
- Spectrum of hadrons studied.
- Bernard Rabin, PhD has pioneered the field
  - Biggest repository of data on strain, age, ion, dose multiple concomitant domains.

9. ***Cognitive functioning study maturity assessment (HIGH)***



Note full tables are reproduced at the end of this section and can be found in expanded form in Appendix C

10. ***Arousal & Regulatory study maturity assessment. (MOD- data being accrued)***

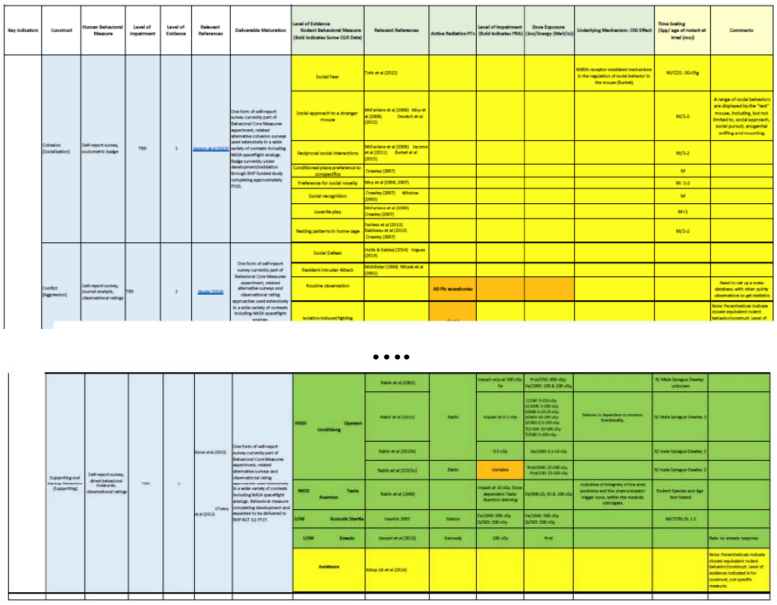


Key Indicators	Construct	Human Behavioral Measure	Level of Impairment	Level of Evidence	Relevant References	Deliverable Maturation	Level of Evidence Rodent Behavioral Measure (Bold Indicates Some CGR Data)	Relevant References	Active Radiation PI's	Level of Impairment (Bold indicates PRA)	Dose Exposure (Ion/Energy (MeV/n))	Underlying Mechanism: CNS Effect	Time Scaling (Spp/ age of rodent at irrad (mo))	Comments
Operational Task Performance (e.g. robotics, vehicle control, EVA, contingency scenarios, dual	Robotics Operation	ROBoT			http://nix.nasa.gov/search.jsp?R=20130012678&qs=N%3D4294916663	Currently part of Behavioral Core Measures experiment								
	Vehicle Control and EVA	MMSEV Flight Simulator				Currently in use in HERA								
Arousal and Regulatory (e.g. sleep, circadian phase)	Sleep duration	Actigraphy	TBD: general recommendation of 7-8 hours a night, but individual differences exist	1	Barger et al. (2014)	Extensively validated as indirect measure sleep duration in ground studies and on ISS; high TRL/CRL. Less direct than EEG	LOW Actigraphy Sleep island		Davis					
	Sleep architecture	EEG	TBD: persistent changes (e.g. reduction of) sleep stages	1	Dijk et al (2001)	EEG and PSG used extensively on the ground; small n of PSG	LOW EEG	Wellman et al (2016)	Britten (Prelim)				R/9	
	Circadian Phase (predicted)	Actigraphy	TBD	2	Flynn-Evans et al (2014)	Uses Jewitt model and actigraphy data to estimate whether circadian trough is in wakefulness or during sleep.	LOW Actigraphy		Davis					
	Circadian Phase	6-sulphatoxymelatonin (aMT6s), collected every 2 to 8 hours over a 24-to 48-hour period	TBD	1	Benloucif et al. (2008)	Extensively validated as estimate of melatonin production. Not used in flight yet, but will be incorporated in upcoming ISS study Lighting Effects. More direct than modeling.	SCN ephys Biochem markers							

11. ***Individual Behavior State study maturity assessment. (Tricky)***

Key Indicators	Construct	Human Behavioral Measure	Level of Impairment	Level of Evidence	Relevant References	Deliverable Maturation	Level of Evidence Rodent Behavioral Measure (Bold Indicates Some CGR Data)	Relevant References	Active SRE PI's	Level of Impairment (Bold indicates PRA)	Dose Exposure (Ion/Energy (MeV/n))	Underlying Mechanism: CNS Effect	Time Scaling (Spp/ age of rodent at irrad (mo))	Comments
Individual Behavioral States (e.g. mood, stress, anxiety/fear, separation/loneliness, frustration/boredom, motivation)	Stress	Visual Analog Scale				Currently part of Behavioral Core Measures experiment	Immobilization	Pitman et al (1988) Ostrovnov et, 2014				Corticosteroid increases	R/Male Long Evans: 2	
	Depression	Beck Depression Inventory (BDI-II)			Beck (1972)	Currently part of Behavioral Core Measures experiment	Forced Swim Test	Castagné et al (2011)						
							Inescapable Shock	Wellman et al (2016)						
							LOW Sucrose Preference (Anhedonia)	Britten et al (2014)	Britten	None	Fe/1000: 20 cGy			
							Tail Suspension	Castagné et al (2011)						Mind-body suspension studies. No reports?
							Social Defeat	Hollis et al (2014) Irigaki (2014)	Limoli, Ebsh?					
							Learned helplessness Novelty-Suppressed Feeding		Limoli, Ebsh?					
	Mood	Profile of Mood States - Short Form (POMS-SF) Zung Self-Rating Depression Scale Hamilton Rating Scale for Anxiety (HAM-A) Beck Scale for Suicide Ideation (BSI) and Beck Hopelessness Scale (BHS) Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) Psychological General Well-Being Index (PGWBI) Pittsburgh Sleep Quality Index (PSQI)			Zung (1965) Curran et al (1995) Hamilton (1959) Beck (1974) Beck (1988) Endicott (1993) Dupuy (1984) Ivezen (1999)	Currently part of Behavioral Core Measures experiment	HIGH Elevated Plus Maze	Rabin et al (2015b)	Rabin	0.1 cGy	He/1000: 0.1-10 cGy		R/ male Sprague Dawley; 250g	
							HIGH Changing Reinforcement Schedules	Rabin et al (2011)	Rabin	Dose and ion specific. Impacts on ability to deal with changing reinforcement schedules.	C/200: 5-100 cGy O/1000: 5-100 cGy Si/600: 0.10-25 cGy Si/600: 10-200 cGy Si/980: 0.5-100 cGy Ti/1100: 10-100 cGy Ti/600: 5-100 cGy	Depends on functionality of dopaminergic systems.	R/ Male Sprague Dawley: 2	
							HIGH Open Field Avoidance	Pecaut et al (2004)	Nelson	No Impact	Fe/1000: 10, 50 & 200 cGy		M/ Female C57BL/6 mice: 2.5	
	Anxiety						Light-Dark Exploration	Mineur et al (2006); Toth et al (2012)					Mice: 2	
							Light-Dark Exploration	Mineur et al (2006); Toth et al (2012)					Mice:2	
							Vogel Conflict Test	Crawley (2007) Blanchard et al (2003)						
							Marble Burying	Crawley (2007)						
							Unpredictable Chronic Mild Stress	Mineur et al (2006)					Mice:2	

12. ***Social Processes study maturity assessment. (Ripe for picking)***



13. ***Interim Conclusions***

- Cognitive Functioning.
  - Potential GCR effect. A few (imp) HFBPE constructs remain to be studied. Need to study co-variant effects, establish mechanisms and develop countermeasures.
- Arousal and Regulatory.
  - GCR data accruing. Need to study co-variant effects (does GCR diminish effectiveness of HFBP countermeasures).
- Individual Behavior states (Tricky & Complex)
  - Rodent tasks are available (components) and data available.
  - Need to capture anecdotal data.
- Social Processes.
  - Data needed. Multiple tasks are available (only supporting behavior has been studied).
  - Need to capture anecdotal data.

14. ***Co-Variants that may need studying***

1. A. Sex differences
1. B. Strain differences (just one species? But 21CFR314)
2. A. Sleep and Stress
2. B. Circadian effects (testing)
3. Hypercapnia
4. Degree of Entrainment.
5. Pre-selection/Resilience
6. Diet

These are big studies to undertake! Too big for a single lab?

- Other formal studies needed

1. Single/Multiple constructs
2. Quirky Behavior (meta-analysis/database)

15. ***Most cost effective ways to achieve goals?***

NASA wants Y/N answers to "***is there a problem?***"
If "Yes" then "how do we fix it?"

Priorities - What is the most important thing to fix?
Time - Need to fix highest priorities ASAP
Regulatory - Fix needs to "legal"
Logistics - BNL & PIs
Cost

When NASA wants Y/N answers to "***is there a problem?***"
Mechanistic studies are **NOT** needed.

When NASA wants to know "***how do we fix a problem?***"
Mechanistic studies **ARE** needed.

Intelligent countermeasures can be developed.
"OTC [over the counter]" Countermeasures can be screened (e.g. BARDA).

16. ***Acknowledgements Dr. Jason Schneiderman***

- Dr. Lauren Leveton
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- Diana Arias
- Jessica Burkett
- Elizabeth Young

Charge to Workshop

Charge to the Workshop
G Nelson, 6/13/17

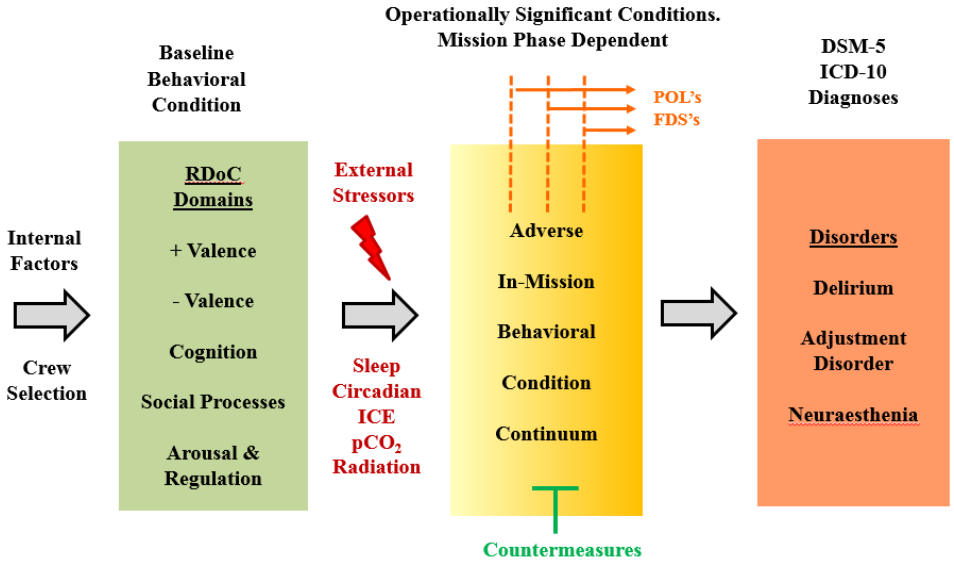
1. *Goal.*
Develop a consensus for a standard test battery of cognitive and behavioral tests that:

1) support validated translation between animal models and humans,
2) are conducive to testing impairment due to spaceflight stressors, and
3) are conducive to evaluating mission acceptable countermeasures.

2. *Objectives*

- Review evidence for radiation-induced changes in animal outcome measures and assess relevance to changes in human outcome measures important to spaceflight.
- Identify the most relevant and valid performance characteristics for each outcome measure and identify the key underlying biological processes and structures in animal models (proxies) that translate with high confidence to human outcome measures.
- Recommend best practices for translating animal measures to human measures in order to estimate their influence on permissible outcome limits or operationally significant degradation of performance.
- Rigor of experimental methods.
- Validation strategies to identify degree of concordance.
- Risk associated with premature standardization/translation.

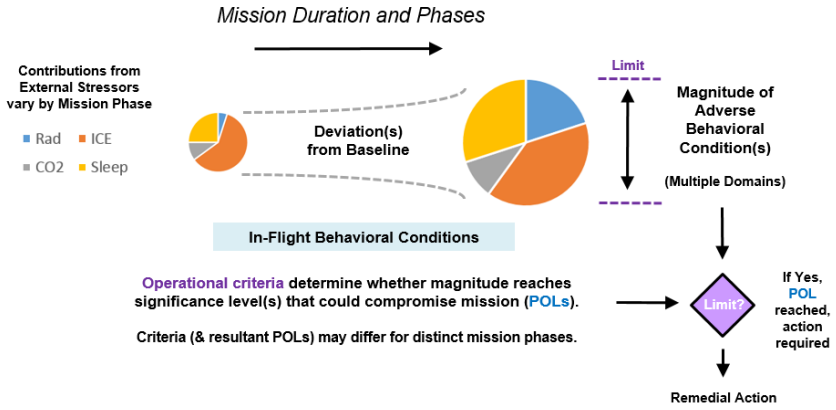
3. *Permissible Outcome Level to Permissible Exposure Limit Estimation (1)*



4. *Permissible Outcome Level to Permissible Exposure Limit Estimation (2)*

Adverse Behavioral Conditions Develop as a Consequence of Interactions between Internal and External Factors

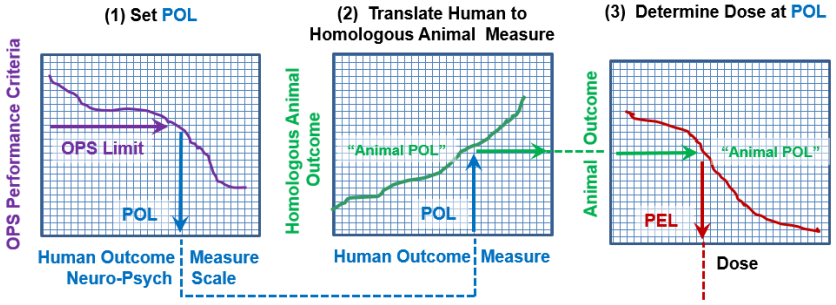
They will depend on mission phase and duration.



Logic for Establishing PELs

PEL = f(POL)

Combine Evidence from Validated Animal – Human Translational Models

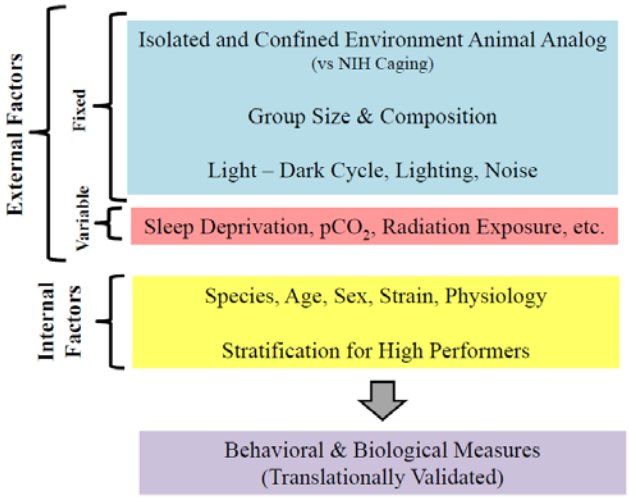


Performance level (POL) established by OPS criteria for limit at which adverse behavioral condition may affect mission.

Establish animal performance value in outcome measure homologous to Humans at POL

PEL = Dose at which animal homologous outcome measure reaches value equivalent to human POL.

5. *What Standard Experimental Conditions are Needed?*



6. *Suggested Discussion Questions (1)*

- Can effects of identified human spaceflight stressors on cognitive and behavioral outcome measures be tested in animal models such that combined effects of radiation and secondary stressors be evaluated?
- Are there potential "reference stressors" that could be used as standards for assigning levels of significance to radiation-induced changes that would guide translation of results to humans? (e.g. equivalent blood alcohol levels, degree of sleep deprivation, etc.). How would effects of reference stressor best be measured in rodents and humans?
- How well do animal model and human mission-relevant outcome measures correlate?
- Are current animal models adequate or would research benefit from new or improved (standardized) animal models? Are NHPs needed?
- What is needed to bridge the translational gap between animal models and human behavioral assessment?

7. *Suggested Discussion Questions (2)*

- What are validation criteria for translatability and does the suite of identified models provide sufficient cross validation of measured outcomes?
- Is the use of multiple models employing different approaches to provide converging evidence a requirement?
- What are the relevant translational models from the Research Domain Criteria neurocircuitry systems?
- If rodent models do not simulate all aspects of a complex, cognitive process, how can we isolate, identify and interpret underlying perturbations in functional neurocircuitry?
- Could the effectiveness of countermeasures, including exercise, diet, pharmaceuticals, and training, be tested and validated in the identified suite of models?

8. ***Impediments to Risk Estimation***

- Valid methods for extrapolation to humans
- No accepted definitions of “significant impairment”
- Non-linear dose responses across space radiation dose domain
- Dose, dose rate and ion species dependence
- Not monotonic with LET
- Brain region specific responses
- Physical target not well defined
- Interactions with other space flight factors

9. ***Minimum Effective Doses.*** Acute dose rate single ion experiments in rodents

Protons: 25 cGy psychomotor vigilance test, 50 cGy neurogenesis; 10 cGy oxidative stress in cultured neuroblasts; 10 cGy altered microvessel adhesion proteins; 100 cGy inflammatory markers; 10 cGy dendritic spine number; 50 cGy hippocampus microvessel number and structure; 2 cGy gene expression changes (gammas).

HZE: 15 - 25 cGy attentional set shift; 20 cGy taste aversion; 25 cGy operant conditioning with one report at 1 cGy for ^{16}O; 20 cGy Barnes maze; 5 cGy ^{48}Ti and 30 cGy ^{16}O novel object recognition; 50 cGy neurogenesis; 10 cGy contextual fear conditioning; <10 cGy oxidative stress in cultured neuroblasts; 5 cGy dendritic spine number; 50 cGy hippocampus microvessel number and structure; 50 cGy endothelial sheet barrier function; 50 cGy brain surface microhemorrhage; 10 cGy synaptic excitability; 25 cGy long term potentiation (synaptic plasticity); 100 cGy amyloid plaque deposition in transgenic mice

Current Permissible Exposure Limits

The CNS PELs correspond to the doses at the hippocampus, and are set for time periods of 30 days, 1 year, or a career, with values of 500, 1000 and 1500 mGy, respectively and an additional PEL requirement for particles with charge Z >10 that limits the physical dose for 1 year and career to 100 mGy and 250 mGy, respectively.

Short Presentation by Richard Britten

Snapshot of Evidence that Executive Function (cognitive flexibility) is impaired following GCR exposure.

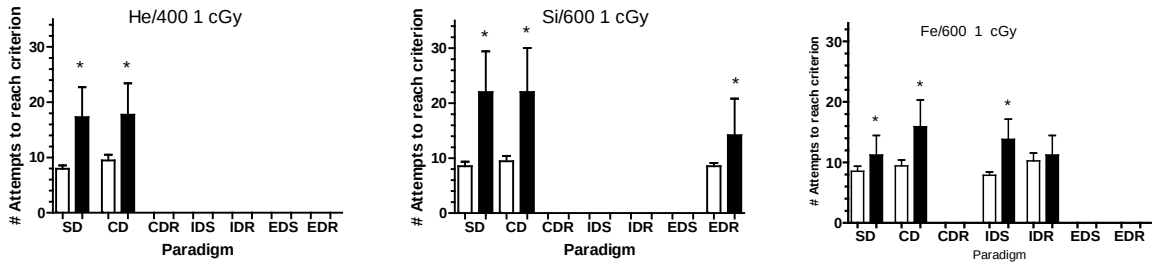
What is executive function?

- A set of higher order cognitive abilities that animals utilize to process external environmental cues and achieve a desired goal in the most efficient and acceptable way. Problem Solving
- Executive functions utilize multiple processes involved in planning, organization, decision making, judgment, task monitoring, attention, problem solving, hypothesis generation, abstract thinking, and cognitive

Cognitive Flexiblity

- Cognitive flexibility is the capacity to inhibit a dominant response when it represents a non-optimal or inappropriate solution and to enable access to more remote alternatives
- To date, rodent models have examined this executive function with the use of the ATSET task (constrained).
- Problem solving in humans often involves unconstrained cognitive flexibility, - develop novel solutions (insightful problem solving).

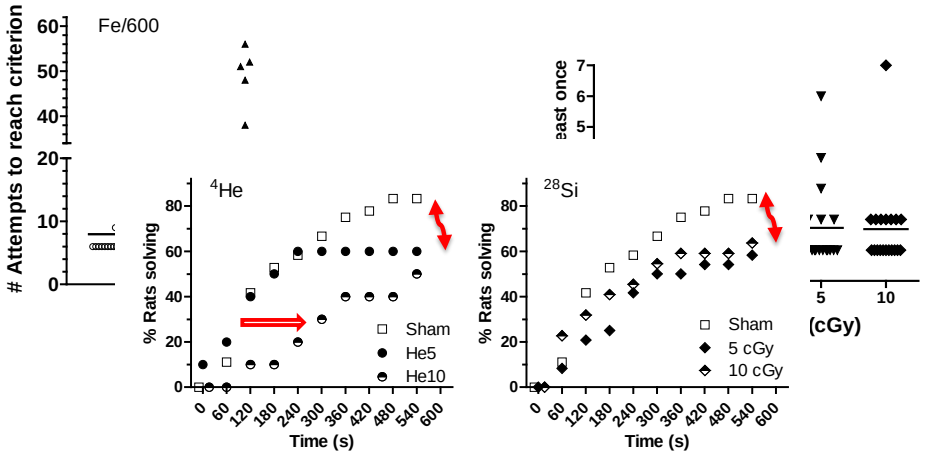
Low (<5 cGy) GCR impair ATSET performance.



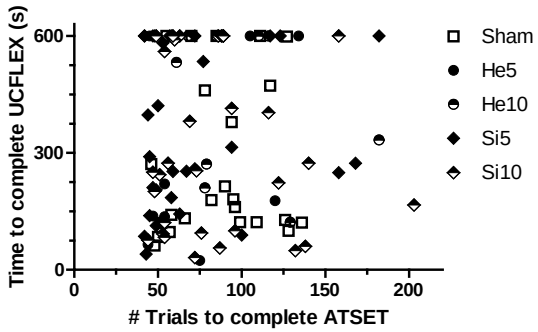
Probabilistic Risk Assessment- Severe (PDF) rates

		ATSET stage					
GCR ion & Dose	LET (keV/um)	FF	SD	CD	CDR	IDS	Overall
Sham	-	0%	3%	0%	5%	0%	8%
5 cGy 400 MeV/n ^{4}He	1.3	0%	0%	9%	0%	18%	27%
5 cGy 600 MeV/n ^{28}Si	58	11%	11%	8%	11%	0%	41%
5 cGy 1 GeV/n ^{48}Ti	106	0%	17%	20%	19%	7%	63%
5 cGy 600 MeV/n ^{56}Fe	180	0%	4%	11%	23%	4%	43%

Inter-individual variations in "good" rats… Event critical performance (PSF & PDF)



Low (<5 cGy) GCR impair UCFlex performance. Event & time critical. Some rats can never solve (4 attempts in ATSET). Those that do are slower.



Even within cogflex no consistent co-impairment.

Need multiple metrics for PRA analysis.

Short Presentation by Catherine Davis

What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?

- Sustained attention deficits in rPVT following radiation – differ by individual
  - Human performance: vigilance/sustained attention measured by PVT
- Deficits in 24-hr recognition memory of novel social odor
  - Human performance: recognition memory and social processing
- Stimulus discrimination and reversal
  - Human performance: executive function/cognitive flexibility

Which non-radiation spaceflight factors are amenable to animal based testing? Are there promising approaches for testing their interactions with radiation?

- Sleep restriction and deprivation - rodents used often in the literature
- Hypercapnia – hypoxia and radiation have been used in rats (Barnes maze)
- Microgravity
- Isolation vs. social housing conditions – rodents social animals
- Exercise
- Specific diets
- Circadian disruptions
- When to perform these manipulations?

Can we define a set of core measures and test conditions for animals that translate to human measures?

- With animal subjects, need a behavioral systems approach to defining/designing core measures
    - Determinants of behavior organized by evolutionary pressures, development into distinct systems – e.g., feeding, defense, mating, parenting
    - Behaviors constrained, species typical, individual differences due to selection pressures
- Need to strive for construct validity in the selected animal tests and within-subject designs
- Consistent time points post exposure
- Memory – NOR most commonly used by PIs
- Attention – different tests currently used by PIs measuring different aspects of attention
- Social processing – take advantage of rodents innate social behavior
- Design new behavioral tests when needed

What problem definition and guidance is needed from the HFBP community and external experts?

- How should impairment be defined?
- How to handle variability?
- Should we modify/standardize most common of the currently used tests?
- Should we standardized strain/species used – e.g., every study includes a group of C57 mice, etc.
- Should we assume that radiation will have the same degree of effects as other experimental manipulations (e.g., lesions, knockout, pharmacological manipulations, etc.), such that these animal tests can be used "as is"?

Short Presentation by Amelia Eisch

Experimental highlights and related domains of human performance

Mice (C57BL/6J) Male 6 mon @ IRR
^{56}Fe (frac. 20cGy) 600 MeV/n LET: 174 Kev/um
^{28}Si (20, 100 cGy) 275 MeV LET: 72 Kev/um

Improved operant learning (touch screen). Wide brain areas

Improved pattern separation:
appetitive (touch screen),
aversive (context dependent fear conditioning)
Hippocampus/contextual discrimination

Non-radiation spaceflight factors amenable to animal-based testing and interaction with radiation

- Individual susceptibility
- age at irradiation, sex, stress reactivity, physical and mental health
- Microgravity

Core measures and test conditions for animals that translate to human measures

Table 3 The criteria of validity for animal models.

Kind of validity	*Aspect of validity*	*Object of validity (animal/human similarity of...)*
homological validity	species validity	Species
	strain validity	strain
pathogenic validity	ontopathogenic validity	interaction transforming an initial organism into a vulnerable organism
	triggering validity	interaction transforming an initial or a vulnerable organism into a pathological organism
mechanistic validity		theoretical cognitive or neurobiological mechanisms producing the observable effects of the disease.
face validity	ethological validity	behavioral symptoms of the disease
	biomarker validity	biomarkers associated with the disease
predictive validity	induction validity	relation between the triggering factor and the observable effects of the disease.
	remission validity	relation between the therapeutic agent and the observable effects of the disease.

Belzung and Lemoine Biology of Mood & Anxiety Disorders 2011, 1:9

Problem definition and guidance needed from the HFBP community and external experts

- Reporting (including detailed methods, and particularly negative data)
- Cross-disciplinary strategy engaging multiple aspects of physiology rather than single experiments
- Reproducibility across labs, species, strains
- What is the best "model" for an astronaut?
- Engage non-NASA funded colleagues (senior/junior faculty mentors, etc.)

Short Presentation by Cynthia Lemere

What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?

^{56}Fe Radiation-Induced Changes in WT and AD-Like Mice (IRR at 4 mo; behavior at 12 mo of age):

- Sex-specific results suggest male and female astronauts may respond differently to radiation.
- In particular, males may be susceptible to memory issues.
- Radiation accelerated AD pathogenesis in male AD-like Tg mice but not females.

Which non-radiation spaceflight factors are amenable to animal based testing? Are there promising approaches for testing their interactions with radiation?

- Microgravity effects on CNS function: Pre- and post-flight MRI for fluid shifts and long-term effects on behavior.
- Pre-treat mice with radiation before microgravity and vice versa?
- Sex-dependent differences in spaceflight visual impairment
- Role of inflammation in all of the above

Can we define a set of core measures and test conditions for animals that translate to human measures?

- Locomotion (Open Field, Y maze, Elevated Plus Maze)
- Motor coordination and motor learning (Rotarod)
- Muscle strength and fatigue resistance (Grip Strength and Wire Hanging)
- Learning and exploration (novelty Y maze, novel object recognition, CFC)
- Memory (Y maze, Contextual Fear Conditioning – including memory extinction)
- Anxiety and depression (Elevated Plus Maze, Tail Suspension, Open Field)
- Sensorimotor reactivity and gating (Acoustic Startle and Pre-pulse Inhibition)

What problem definition and guidance is needed from the HFBP community and external experts?

Differences between rodents and humans:

- Life span (especially investigating aging effects)
- Immune system
- Difficult to know what a mouse/rat is feeling or learning or remembering
- Visual impairment in rodents difficult to assess?
- Genetic variability in humans

Mice live in pathogen-free environments

Short Presentation by Charles Limoli

What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?

- Persistent (1 year) behavioral decrements in a variety of open field exploration tasks, elevated anxiety and depression like behavior, deficits in cognitive flexibility, fear extinction that span multiple regions of the brain.
- Persistent (permanent?) reductions in dendritic complexity and spine density, that are temporally coincident with poor behavioral performance, elevated neuroinflammation (activated microglia) and changes in microcircuit and large scale network connectivity.
- Differential radiosensitivity of neurons in various regions of the brain, raising questions about critical CNS targets and their assumed impact on radioresponsive endpoints.
- Role of retrograde endocannabinoid signaling
- Activated microglia as a "permanent" inflammatory signature (M1 vs M2; A1 vs A2, SASP)

Which non-radiation spaceflight factors are amenable to animal based testing? Are there promising approaches for testing their interactions with radiation?

- The impact of preconditions (prior training, metabolic, inflammatory baselines)
- Mood disorders
- Microgravity – via hindlimb unloading
- Impact of sleep disruption
- Sex differences – pathway engagement (circulating vs endogenous of hormones etc.)

Can we define a set of core measures and test conditions for animals that translate to human measures?

Yes –

- Learning and memory deficits as they relate to cognitive flexibility (increasing task rigor (represent a few (e.g. Fear extinction, attention set-shifting, odor sequence tasks, platform relocation tasks).
- Mood disorders - anxiety (light/dark transitions mazes), depression tasks (force swim task)
- Structural and synaptic plasticity, changes in myelination
- Social interaction tests – may be more difficult to interpret
- Spontaneous exploration tasks – search for novelty
- Risk taking behavior, decision making

What problem definition and guidance is needed from the HFBP community and external experts?

- Countermeasures (behavioral, pharmacologic)
- The influence of non-CNS targets – whole body irradiation and the immune response
- Details on astronaut specific tasks
- The impact of preconditions (degree of training, metabolic, inflammatory baseline)
- How are emergencies (unanticipated situations) dealt with in terms of human/computer interfaces
- Things not to dismiss:
    - Animals are absolutely required needed for radioresponsive mechanistic assessments
    - Mechanism is in turn required for evidence-based countermeasure development

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Short Presentation by Bernard Rabin

Highlights from Project NNX16AE06G: "Individual Differences in the Neurochemical and Behavioral Response to Exposure to HZE Particles".

Overall Purpose:

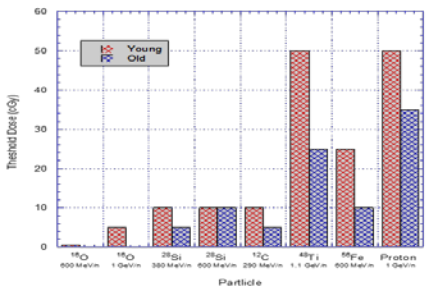
To determine the effects of exposure to HZE particles on neuronal function and cognitive performance and how changes in these end-points are related to individual characteristics (age and sex) and to the characteristics of the specific HZE particle (linear energy transfer).

Approach:

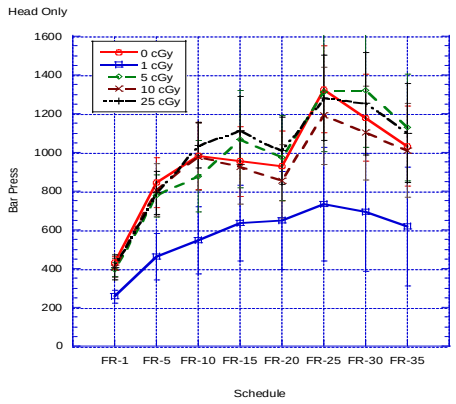
Behavior: Performance is measured to evaluate HZE particle-induced changes in a broad spectrum of cognitive tasks (novel object recognition, operant responding) in young and old individuals

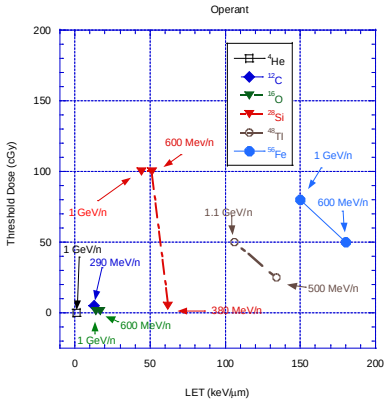
Neuronal Function: Measure the levels of NOX2 (oxidative stress) and COX2 (neuroinflammation) in specific brain regions and cognitive performance.

Threshold (lowest effective dose) producing disruption of novel object recognition performance (a measure of the ability of the organism to remember a familiar object) as a function of age of testing and particle.



Examples of head only, body only and whole body for Operant Conditioning after iron particle irradiation with surprising effectiveness of 1 cGy vs 5, 10 & 25 cGy. (Left). Examples of dose threshold versus particle LET for multiple particle and ion combinations. (Right)





Short Presentation by Jacob Raber

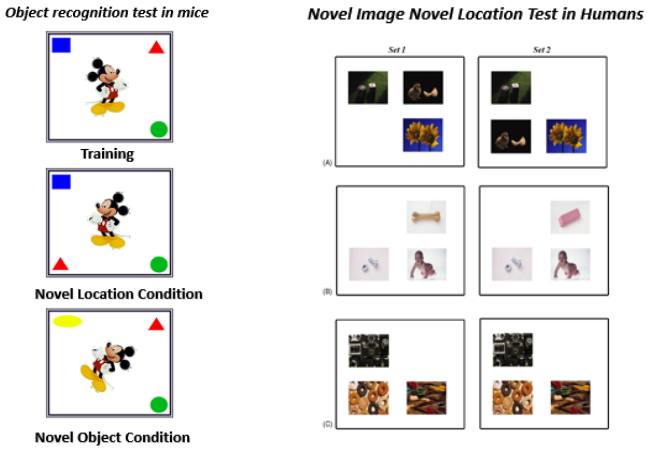
What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?

1. Identification of sensitive behavioral and cognitive translational measures of the space radiation response
2. Identification of pathways associated and correlated with cognitive injury using unbiased approaches.
3. Behavioral performance and cognitive performance

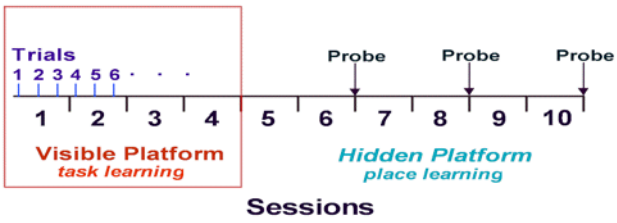
Which non-radiation spaceflight factors are amenable to animal based testing? Are there promising approaches for testing their interactions with radiation?

1. Environmental stressors other than radiation pertinent to astronauts during missions.
2. Genetic and epigenetic factors.
3. Role of age and gender.

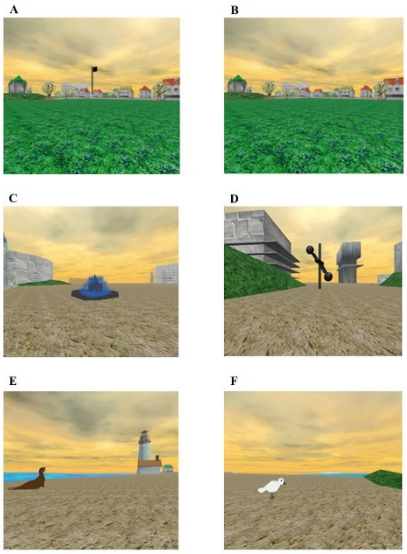
Example of Novel Object Recognition Homologs for Rodents and Humans



Spatial learning and memory navigational test in mice



Spatial learning and memory navigational test in humans
(Memory Island)



Can we define a set of core measures and test conditions for animals that translate to human measures?

Yes, we can take tests shown to be sensitive to effects of space irradiation and for some of which translational human tests are available; two example we have used are object recognition/NINL and spatial learning and memory requiring navigation/Memory Island.
However, important considerations not to do this:

1. Our combined collective knowledge is mostly based on single beam irradiations and not mixed beam irradiations.
2. Our combined collective knowledge is mostly based on acute and not chronic irradiations.
3. Our combined collective knowledge does not necessarily involve yet environmental conditions/stressors other than space irradiation.
4. Our combined collective knowledge supports that while some test might be particularly sensitive to detect effects of space irradiation, there are definitely radiation quality-dependent effects on measures, even in the same test.
5. Performance on behavioral tests can be affected by the environmental conditions during the test and condition of the animal/human.
6. Ability of a cognitive test to detect effects of space irradiation will likely depend on the version of the cognitive test used; amount of training, interval between training/learning and memory assessment, difficulty level, etc
7. Lessons learned from validity criteria for animal models of neurological and psychiatric conditions; face, predictive, and construct validity elaborated by Wilner. Pertinent and

valuable animal tests might look very animal specific but incredibly valuable for understanding and treating brain functions in humans.

8. Limited understanding about mechanisms underlying effects of space irradiation, especially mixed beam space irradiation on the brain. This knowledge can guide us assessing pertinent brain functions (bi-directional approach).

What problem definition and guidance is needed from the HFBP community and external experts?

Valuable information from HFBP community:

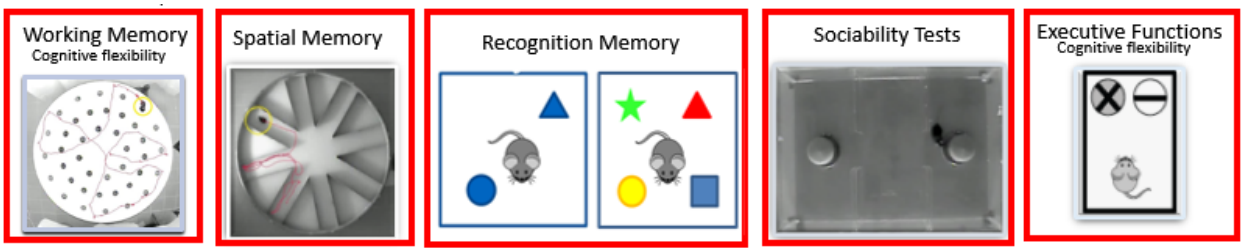
1. More sharing about focus of data acquisition, data analyses, and interpretation.
2. More sharing about long-term concerns based on astronaut data.

Short Presentation by Susanna Rosi

What are the important experimental highlights from your area of expertise and what domains of human performance are they likely to impact?

Cognition (in non-human animals):

- Is inferential- never observed directly, but inferred from changes in behavior.
- Is encoded at synapses of cells activated by an experience.
- Is a network phenomenon.



Behavioral health that account for social disturbances to this extent we have data on two sets of tests that encompasses higher cognitive functions in mice and that can be translated to humans.

- Recognition Memory, Social Memory and Sociability.

- Chronic exposure to galactic cosmic rays cause functional impairments in Recognition Memory, Social Memory and Sociability.

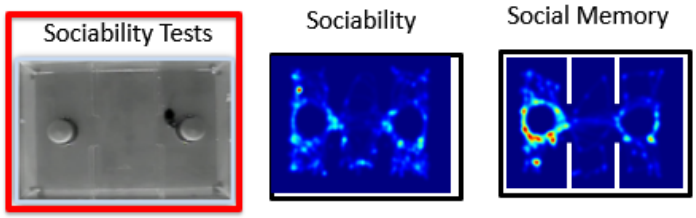
- Test potential countermeasures suitable for spaceflight. By giving a countermeasure (Phase II clinical Trial) after space radiation we were able to prevent the development of the long term deficits.

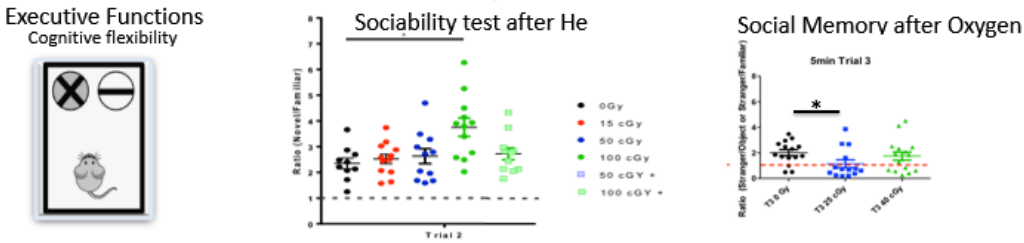
Which non-radiation spaceflight factors are amenable to animal based testing? Are there promising approaches for testing their interactions with radiation?

Cognition: Behavior, Synaptic Function, Network Function, Age, Gender, Countermeasures

Can we define a set of core measures and test conditions for animals that translate to human measures?

Recognition Memory
Sociability
Social Memory
Mental Flexibility

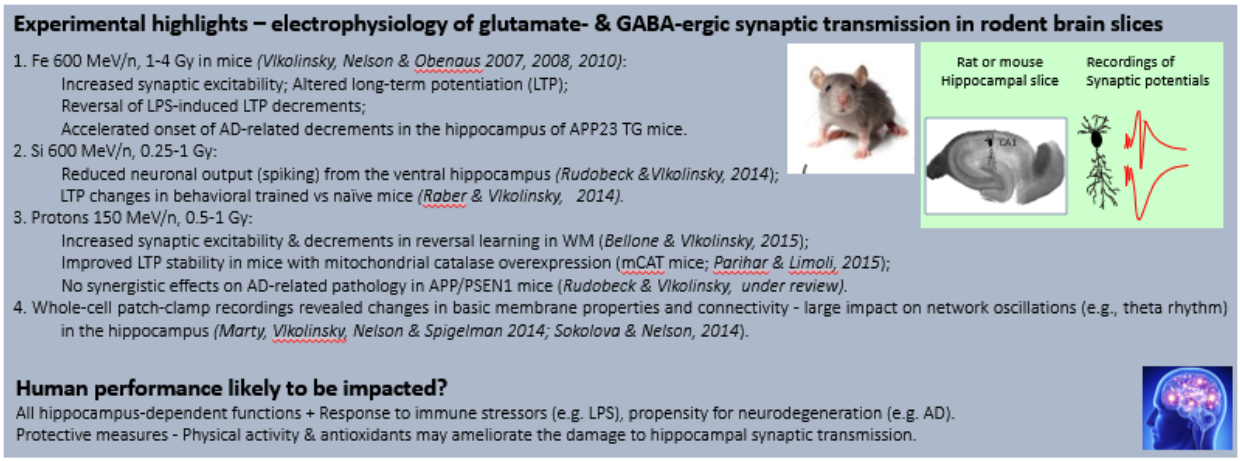




What problem definition and guidance is needed from the HFBP community and external experts?

Determine gold standard predictive tests in humans, are there standard test that can not only evaluate the current mental status but that can predict the possible development of future cognitive decline or susceptibility?
From these we can determine the translatability in rodents.

Short Presentation by Roman Vlkolinsky



Which non-radiation spaceflight factors are amenable to animal-based testing?

1. Microgravity – tail suspension tests; 2. Psychological stressors - solitary confinement.

Are there promising approaches for testing their interactions with radiation?
Electrophysiological techniques *in vitro & in vivo* can test for functional decrements in the above scenarios.

Can we define a set of core measures and test conditions for animals that translate to human measures?
Applicable electrophysiological tests:

1. Circadian activity in Suprachiasmatic Nucleus (SCN) *in vitro* - Note different circadian activity in rodents vs humans;
2. Neuronal memory allocation (Hippocampus) - Place cells activity in the hippocampus *in vivo;*
3. Synaptic memory allocation (Hippocampus) - Synaptic input specificity *in vitro*;
4. Neuronal connectivity:
    - Microcircuit connectivity *in vitro* (any brain area): Patch-clamp paired recordings – e.g., CA3-CA1 neurons; excitatory *vs.* inhibitory neurons;
    - Long-distance projections (e.g., HPC to mPFC) - local field potentials (LFP) analyses *in vivo;*- optogenetic manipulations of the circuits + *in vitro* electrophysiology.

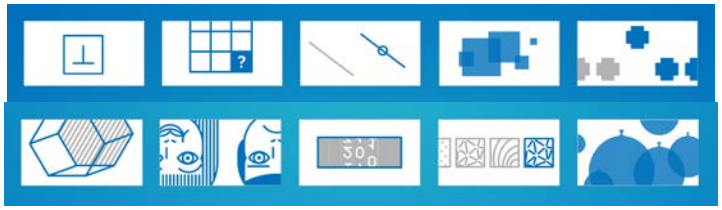
What problem definition and guidance is needed from the HFBP community and external experts?
To be determined at/after the meeting.

Short Presentations by Human Factors and Behavioral Performance Investigators

Short Presentation by Ruben Gur

NASA SR-HFBP Standard Measures Workshop presentation by Ruben Gur representing:
M. Basner[1], D.F. Dinges[1], J. Nasrini[1], S. McGuire[1], E. Hermosillo[1], A.J. Ecker[1],
D.J. Mollicone[2], T.M. Moore[3], and R.C. Gur[3]

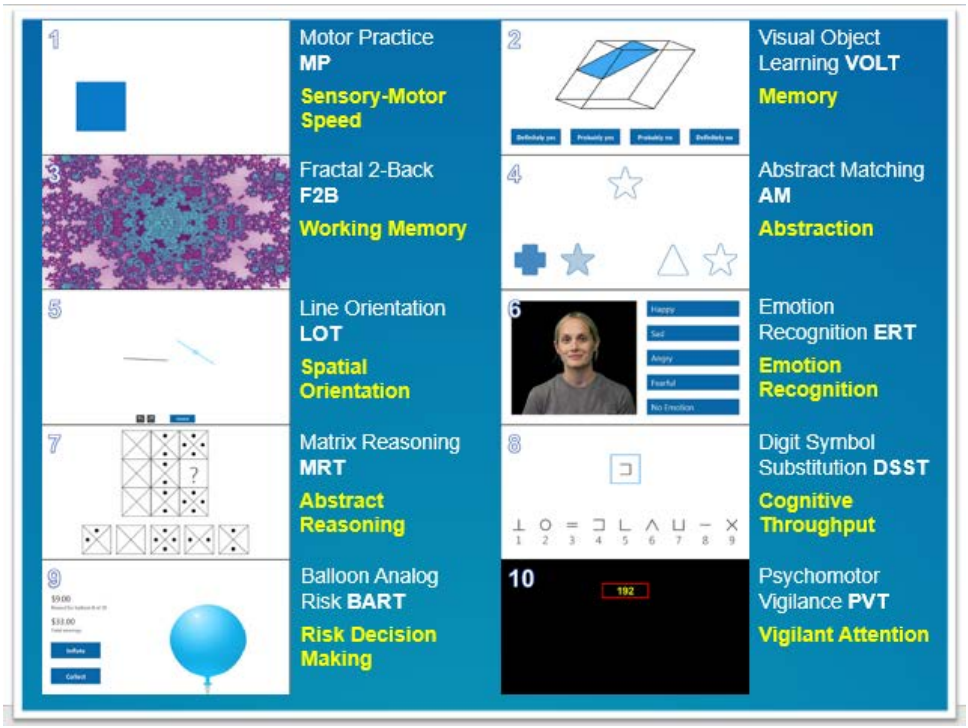
[1]*Division of Sleep and Chronobiology, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*
[2]*Pulsar Informatics, Inc., Philadelphia, PA, USA*
[3]*Brain Behavior Laboratory, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

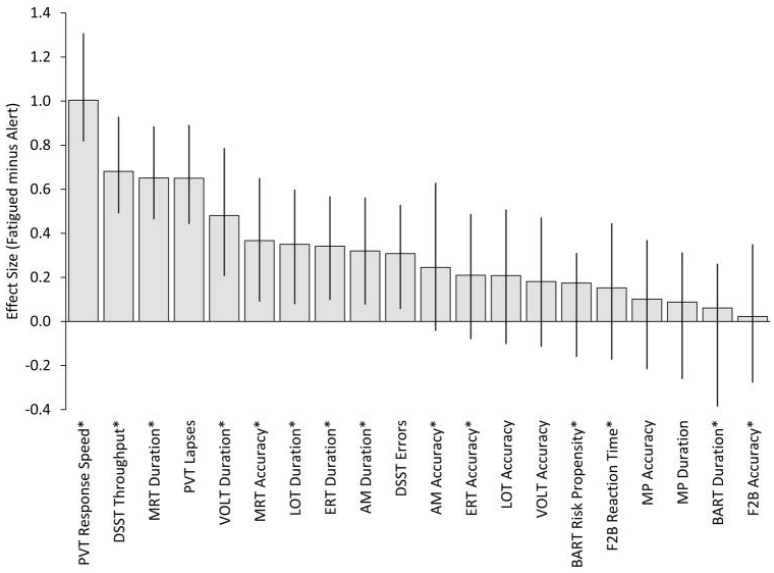


"Cognition" Test Battery

- 10 tests
- Brief (< 20 min)
- Developed for high-performing astronauts
- Covering a range of cognitive domains
- With links to cerebral networks established with fMRI
- 15 unique versions for repeated administration

- **Aerospace Medicine and Human Performance 2015: 86(11)**





Short Presentation by Gregory Light

Assessing the Engagement of Functionally Relevant Neural Systems in Early Stage CNS Development Programs

What principles and strategies best establish the validity of translational models and how can we apply them to NASA's special circumstances?

Use some tasks that can be automatically evoked in the background, in the absence of directed attention, even while subjects performing other tasks
Use some tasks that are *direct* probes of CNS function (i.e., EEG, evoked potentials)
Well-established animal models that are *relatively* easy to setup
All tasks should:

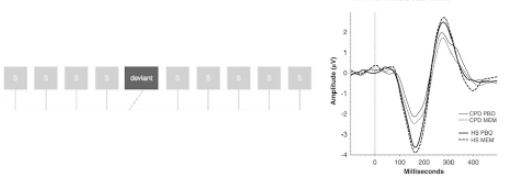
- have well-established short and long-term (e.g., 1-year) test-retest reliability
- be suitable for use as a repeated measure – no practice effects
- be appropriate for study in high-performing individuals, not prone to boredom or other task demands that could interfere with measurement/outcomes
- have consistent robust relationships to important domains of perceptual, cognitive, clinical, and psychosocial functioning
- show *early* and dose-dependent sensitivity to pharmacologic, nonpharmacologic, or other perturbations (i.e., radiation), even after initial exposure. Such early malleability may predict functional deterioration from continued exposure or benefits from countermeasures

Using EEG to Characterize Pharmacodynamics

- Plausible dose response curves
- Minimum dose needed to reliably impact measures
- Characterization of within-subject dynamics
- Characterize psychometric properties and calculate effect sizes required to detect significant effects for an individual
- Identify predictors of individual sensitivity

Leading EEG Biomarkers of CNS Function & Therapeutics

Mismatch Negativity (MMN): negative-going ERP, evoked when a sequence of repetitive 'standard' stimuli is interrupted by infrequent oddball or 'deviant' stimuli

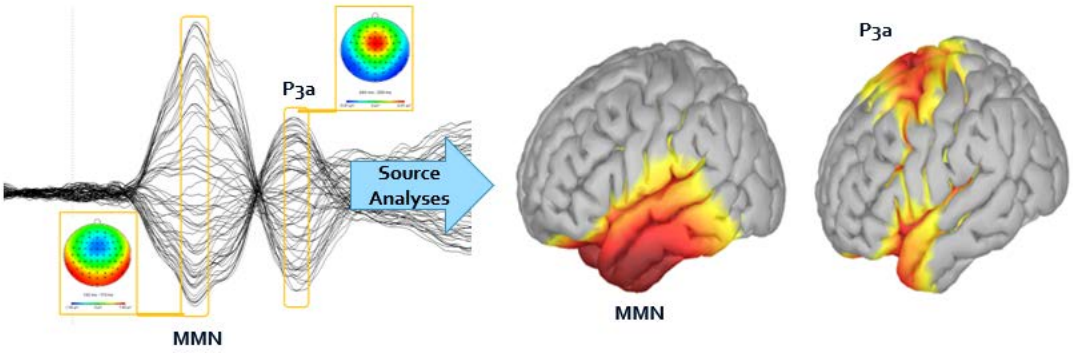


Auditory Steady State Response (ASSR): (γ power, phase locking): stimulus-driven (40 Hz clicks/tones) γ power and synchronization in the EEG, may reflect the capacity of the auditory system to generate oscillations in synchrony with the stimuli.

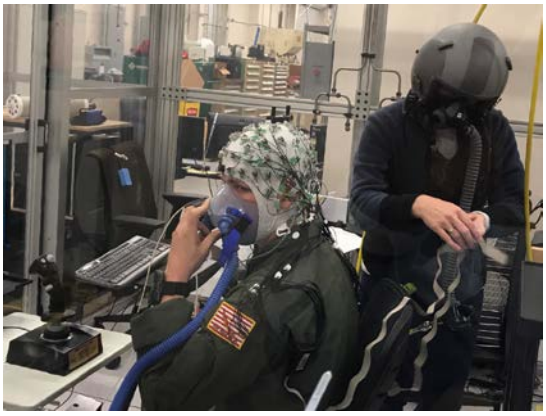
Demonstrating Target Engagement

Drug is:

- Getting into the brain
- Impacting cognitively relevant brain processes
- Showing biologically plausible changes in brain networks



Other Ongoing HFBP Applications



Short Presentation by Peter Roma

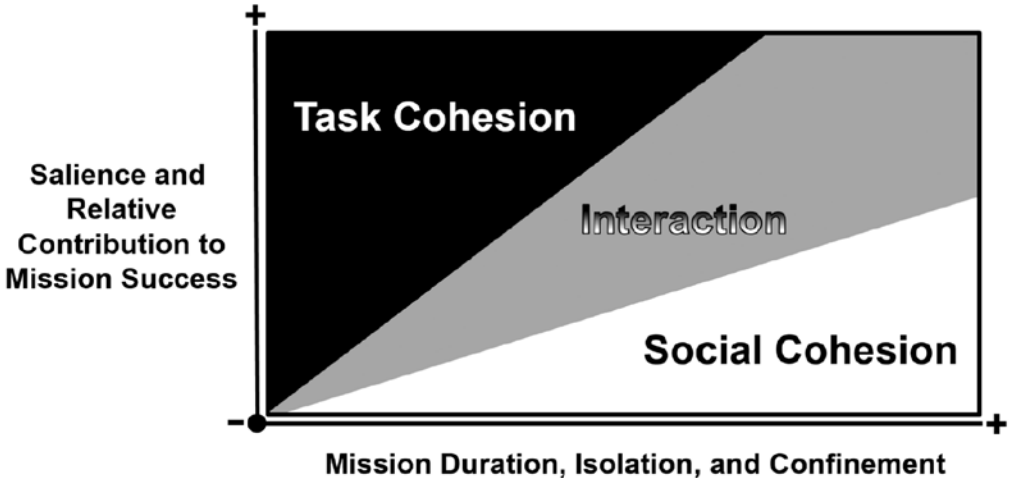
What are the important experimental highlights from your area of expertise and what domains of human performance do they impact?

Extramural grant research focus on team composition, team-level "individual differences," and temporal dynamics of cooperative behavior, social cohesion, and team performance in isolated, confined, and extreme (ICE) environments.

Which spaceflight factors have the greatest potential to negatively impact the domains that you evaluate? Are there promising animal analogs that might enable testing their interactions with radiation?

Mission duration in ICE environments, individual differences in group living competencies, social and romantic relationships, lack of countermeasures to restore team social cohesion.

Fortunately, the passage of time (i.e, lifespan) is much easier to model in animals than to conduct in real-time with humans. Animal analogs of operationally-relevant task and social cohesion processes are limited.



Based on current human data and the R Britten initial assessment, what are the main limitations to evaluation of human impairments and what is needed?

The elephant in the room: We cannot conduct proper experiments in the target species with the independent variable of interest (or even analog thereof), i.e., we cannot experimentally irradiate humans.

What problem definition and guidance is needed from the animal & radiation community and external experts?

Animal analogs (if not homologues) of the standardized measures used in human. Consider "reverse linkage" validation as part of R&D process (i.e., conducting the putatively analogous animal procedures in humans).

Short Presentation by Raphael Rose

What are the important experimental highlights from your area of expertise and what domains of human performance do they impact?

a) Autonomous or self-guided multimedia behavioral health programs can train/treat individuals to improve distress and functioning around common problems such as stress, anxiety, and depression. Components include physiological and emotion regulation, cognitive flexibility, behavioral coping strategies.

b) Areas addresses include stress, resilience, negative and positive affect and impact social processes.

c) Our work has focused on working with high functioning populations (NASA Flight and Mission Controllers, Space Analog-Hi-Seas, UCLA graduate students, UCLA Medical Center Faculty and Students, Air Force Personnel).

Which spaceflight factors have the greatest potential to negatively impact the domains that you evaluate? Are there promising animal analogs that might enable testing their interactions with radiation?

a) Asynchronous Communication, limited habitability, isolation, workload (excessive, repetitive, stimulating?), Danger/trauma

b) Reward seeking and learning, reward responsiveness, and social processes

Based on current human data and the R Britten initial assessment, what are the main limitations to evaluation of human impairments and what is needed?

a) Limited relevant human sample sizes for those working/living in challenging environments

b) More analog and translational research

What problem definition and guidance is needed from the animal & radiation community and external experts?

a) The more the merrier

Short Presentations by External Experts

Short Presentations by Matthew Hoefer & Holly Moore

Extemporaneous remarks on translation techniques and success criteria. No formal presentation.

Short Presentation by Victoria Risbrough

Example: Contextual and Cued Fear Learning and Extinction – Pros for translation

- Constructs – Spatial Memory, Negative valence (threat response, emotion regulation)
- Homologous testing time/requirements: Simple *Automatic* Pavlovian – similar # of trials produce learning across humans
- Probes homologous circuit with high homology across mammals (hippocampus – PFC – amygdala
- Operationalized by both behavioral (self report/expectancy) and physiological readouts (GSR, HR, startle).
- Can discriminate performance via physiology, more sensitive than behavior
- Well characterized associations with specific neuropsychiatric disorders (e.g. trauma-related disorders)
- Affected by sleep, exercise, stress
- Well defined stimulus parameters (e.g US intensity, cue type, etc).
- Well defined theory behind construct (acquisition, extinction, renewal, spontaneous recovery etc.)

Contextual and Cued Fear Learning and Extinction – Cons!

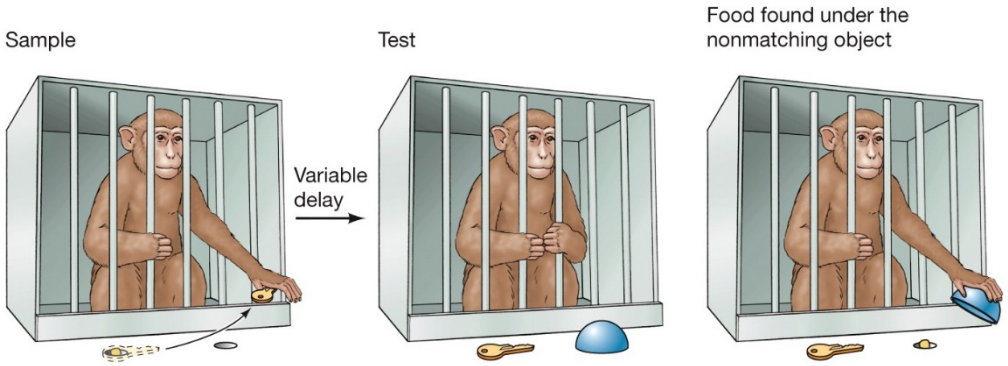
- Limited use within subject, i.e. practice effects (pharmacology studies have used up to 3 times with different stimuli)
- Must consider task carefully to differentiate cued vs. contextual learning (e.g. use configural tasks or trace conditioning to ensure hippocampal specificity).
- Fear learning redundant system, subtle effects will be harder to measure – fear extinction most affected by subtle manipulations

- Individual level changes typically are not assessed, limited (~1000 subjects) normative data available
- Animal test can have a lot of confounding variables – locomotor/exploratory, pain response
- Physiology may not be amenable to testing in space?
- Potential alternates in humans – MST (Stark)

Short Presentation by Craig Stark

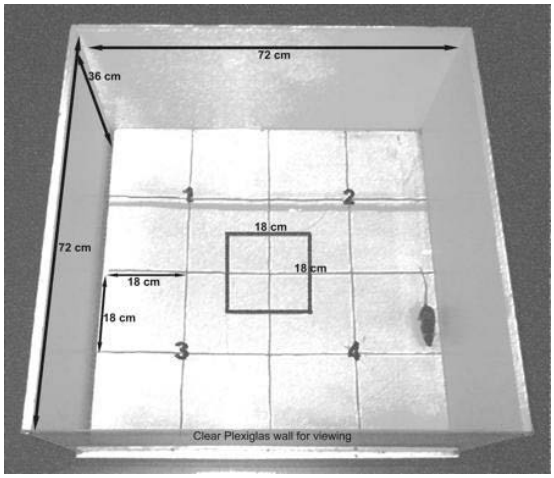
Cross-Species Tests of Hippocampal Function

Traditional approach: Create or find tasks that might mimic the human ability



THE NEUROBIOLOGY OF LEARNING AND MEMORY 2e, Figure 15.4

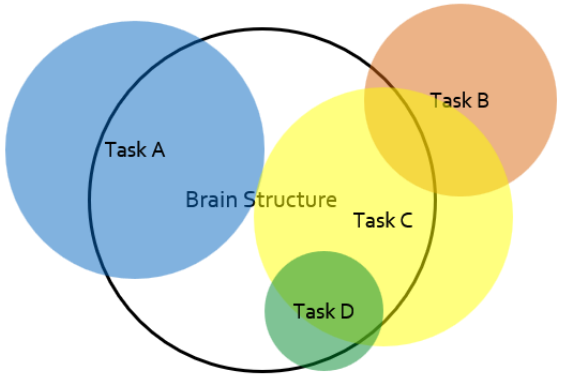
= "Tell me what happened yesterday"



= Ability to leave the house or talk to strangers

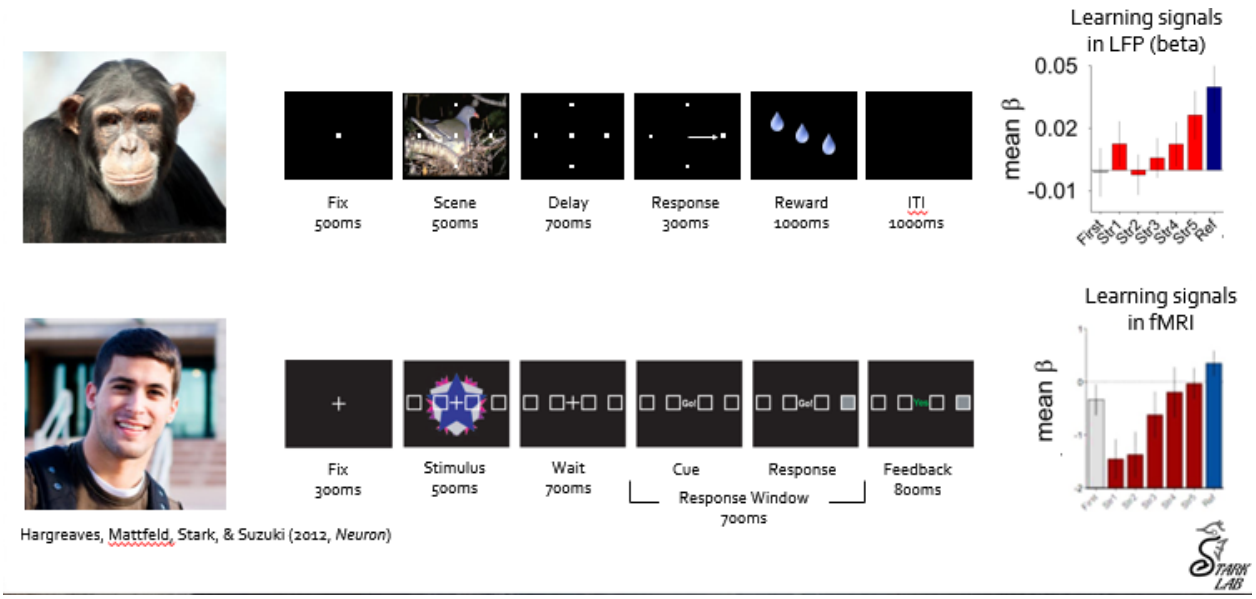
The problem

A: No task is process-pure and it will need things going on outside of that brain structure. It also, quite possibly, won't tap into the entire structure. May not be taxing enough to need it all, may only need some of the computations or sub-structures.
B: So another task – might tap into different aspects of the function and might overall be easier (smaller circle – fewer resources needed) and be more driven by outside structures
C: Another might overlap with what B uses from the structure, but not so much A. So, depending on where / how you affect the brain structure, you might get effects on both B and C, but not A in one situation and A but not B or C in another.
D: Very dependent on the structure and specific to it, but also very "easy" and not needing much of whatever is going on inside there.

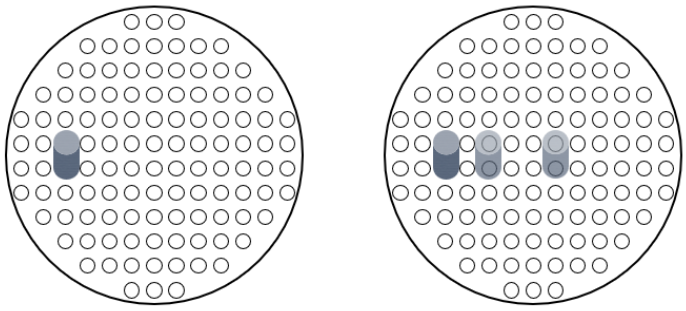


A different approach – create human and animal tasks in parallel.

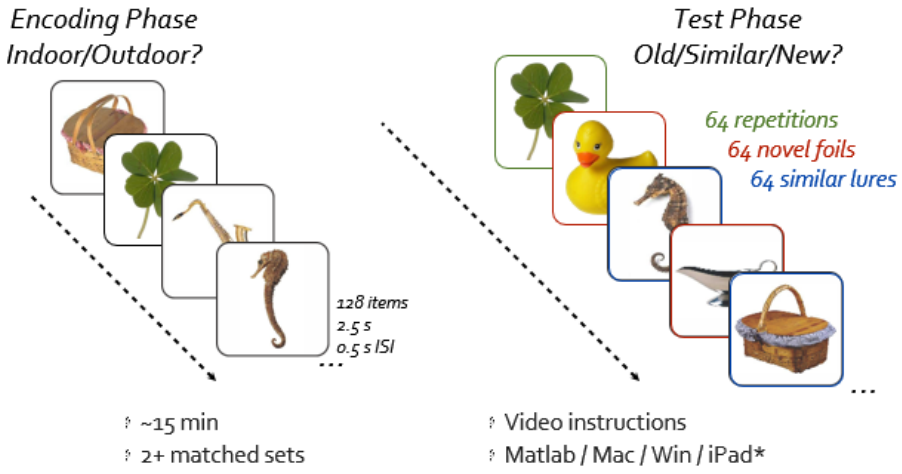
In one preparation – the non-human primate...
In the next preparation – the college undergraduate...



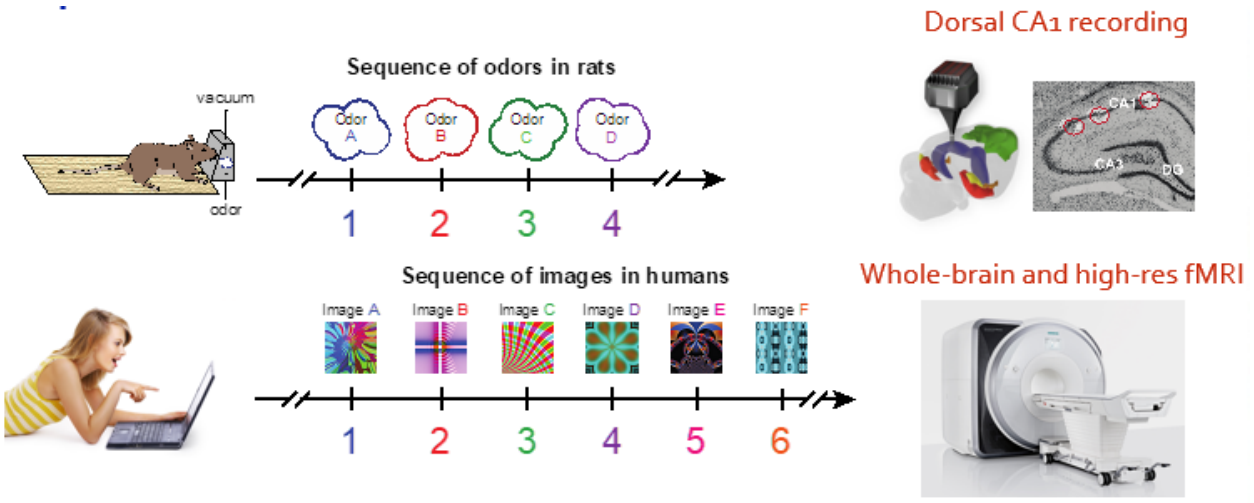
Pattern separation variant of object-location task to hone in on dentate gyrus function



Mnemonic Similarity Task (MST) – Behavioral test of pattern separation in humans.



A cross-species task to study memory for a non-spatial sequence of events.



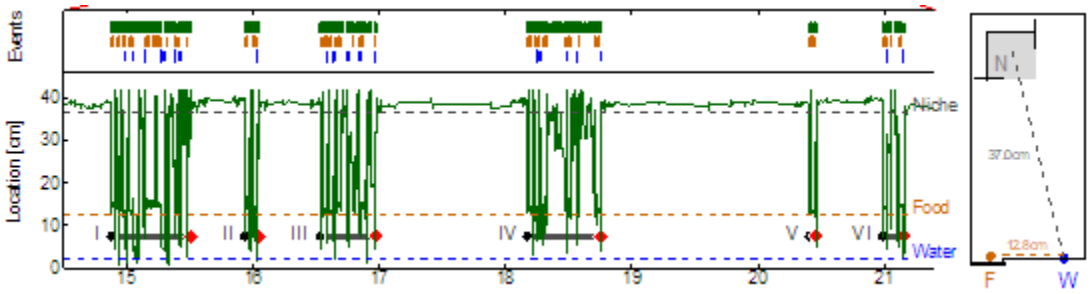
Short Presentation by Lawrence Tecott

Challenges in Behavioral Assessment

- Labor
- Animal handling
- Time of Day
- Behavioral Context

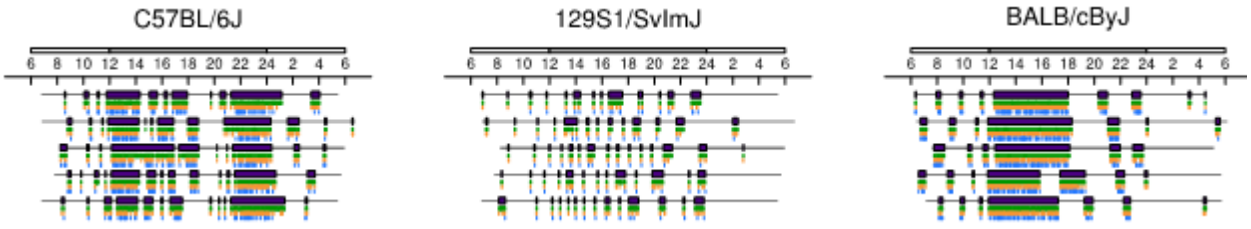
A Systems Approach to Behavioral Assessment: Automating "Ethology"

The Active State Concept



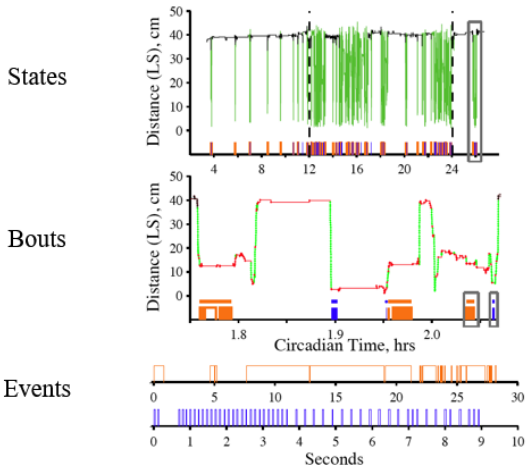
Mouse Phenome Project

Strain Specificity of AS Patterns



Active State Probability Principal Component Analysis

Hierarchical Organization

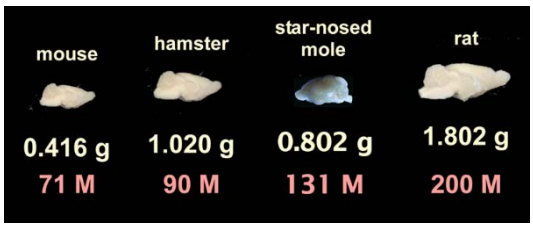


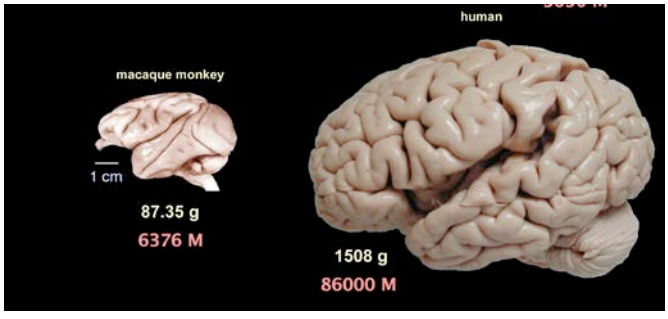
DATASETS

- Serotonin Receptor KO
- ASD Models
- CNS-Active Drugs
- Dietary Fat
- Stress
- Pharmacogenomic Circuit Manipulations

Short Presentation by Robert Turner

- Do we know how well results will translate between species?
- How well does the sensitivity of rodent (brain) tissue to radiation predict that of humans?
  - (Therapies developed to treat TBI in rodents – disappointing translation to humans.)
- Particular focus on the hippocampus: Is the hippocampus / hippocampal function most sensitive to radiation exposure?





Short Presentation by Jared Young

What principles and strategies best establish the validity of translational models and how can we apply them to NASA's special circumstances?

Ultimately, these task/model validations will rely on the cognitive domain of interest
Each task ultimately requires:

1) Internal psychometric validation (e.g., evidence of ID/ED shift in ASST)
2) Test-Retest reliability (longitudinal assessment desired)
3) Preferably coupled with biomarker (e.g., EEG, or PET imaging).
4) For Interpretative requirements, additional motoric/motivational measurements
5) Understanding normal aging + disease aging in normal task performance
6) Understanding circadian challenge effect on normal task performance

What criteria can be used to determine when a space flight environment-elicited change has reached significance in terms of health and performance? Are there animal equivalents?

- Important to differentiate between significant and clinically significant – e.g., animal hippocampal lesions do not impair odor span task performance, while in humans, there is a small but significant (likely semantic) deficit.
- Identifying such differentiation of effects in animals remains difficult, with graded performances (psychometrics needed).
- For example, testing animal in standard paradigm that includes an easy and hard (at limit of capabilities) component. The animal should always perform the easy component and can determine if stress/radiation obliterates difficult component.
- Including biomarkers (e.g., EEG) in animal models are beneficial to determine whether extra cognitive effort exerted even if task performance is maintained. Useful biomarker in space too, for longitudinal assessment.

Based on evidence reports and the R Britten initial assessment, what radiation elicited changes in animals likely impact critical neuropsychological domains in humans?

- Britten et al 2014: Negative consequences of 20 cGy 1 GeV/nucleon ^{56}Fe even on simple discrimination, gradually harder as task gets harder (though not a big reversal effect).
- Britten et al 2016: Even deficits in simple water maze escape learning, supported by poor learning in Barnes Maze.
- Parihar et al 2015: NOR deficits but unclear delay-dependent effects on NOR performance.
- Limitations: Basic assessment of effects on locomotor behavior and/or motivation not assessed (e.g., visual cued water maze or of eating). No psychometrics so unclear why no effect.
- Testing decision making on various reward levels important, including "punishment" to measure punish sensitivity.
- Basic limitations: Using Wistar Rats – Males only – Proven breeders only, why?

Are there a set of core measures that could best be used to translate between animals and humans?

- Ideally, testing would be conducted in tasks that can also be conducted during any flight. For example, although water and Barnes maze is simply, unless virtual reality headgear is brought for testing, it is likely less important.
- Strong concerns of reduced hippocampal neurogenesis can be assessed using delayed-dependent memory. Combining such memory with attentional & response inhibition assessment could be conducted with e.g., AX-CPT.
- Including measurement of physical effortful motivation for motivation assessment plus measuring physical capabilities.
- Excellence of astronauts: What of using outbred mice/rats and testing effects in only the top 3rd….? E.g., Davis et al, 2014 for longitudinal assessment in PV. Can then investigate susceptibility to radiation effects post mortem, conduct circadian challenges, etc.
- For Biomarkers, could include small animal PET for longitudinal assessment on neuroinflammation, or EEG?
- What of testing AD-sensitive animals to determine for early disease progression?

Short Presentation by Jaimie Zeitzer

Extemporaneous remarks. No formal presentation.

Appendix C: Human-to-Animal Mapping Matrix Tables

Report by Richard A. Britten & Stephen Deutsch.

Key Indicators	Construct	Human Behavioral Measure	Level of Impairment	Level of Evidence	Relevant References	Deliverable Maturation	Level of Evidence Rodent Behavioral Measure (Bold Indicates Some CGR Data)	Relevant References	Active Radiation PI's	Level of Impairment (Bold indicates PRA)	Dose Exposure (Ion/Energy (MeV/n))	Underlying Mechanism: CNS Effect	Time Scaling (Spp/ age of rodent at Irrad (mo))	Comments
Social Processes (e.g. communication, bonding, conflict)	Cohesion (Socialization)	Self-report survey, sociometric badge	TBD	1	Santoro et al (2015)	One form of self-report survey currently part of Behavioral Core Measures experiment, related alternative cohesion surveys used extensively in a wide variety of contexts including NASA spaceflight analogs. Badge currently under development/validation through BHP funded study completing approximately FY20.	Social Fear	Toth et al (2012)				NMDA receptor-mediated mechanisms in the regulation of social behavior in the mouse (Burket).	M/CD1: 30-35g	
							Social approach to a stranger mouse	McFarlane et al (2008) Moy et al (2008) Deutsch et al (2012)					M/1-2	A range of social behaviors are displayed by the "test" mouse, including, but not limited to, social approach, social pursuit, anogenital sniffing and mounting.
							Reciprocal social interactions	McFarlane et al (2008) Jacome et al (2011) Burket et al (2015)					M/1-2	
							Conditioned place preference to conspecifics	Crawley (2007)					M	
							Preference for social novelty	Moy et al (2004, 2007)					M: 1-2	
							Social recognition	Crawley (2007) Winslow (2003)					M	
							Juvenile play	McFarlane et al (2008) Crawley (2007)					M<1	
							Nesting patterns in home cage	Fairless et al (2013) Babineau et al (2013) Crawley (2007)					M/1-2	
	Conflict (Aggression)	Self-report survey, journal analysis, observational ratings	TBD	1	Stuster (2016)	One form of self-report survey currently part of Behavioral Core Measures experiment, related alternative surveys and observational rating approaches used extensively in a wide variety of contexts including NASA spaceflight analogs.	Social Defeat	Hollis & Kabbaj (2014) Iniguez (2014)						
							Resident Intruder Attack	McAllistar (1994) Miczek et al (2001)						
							Routine observation		**All PIs anecdootes**					Need to set up a meta-database, with other quirky observations to get statistics
							Isolation-induced fighting Tube test for social dominance		Eisch?					Note: Parantheticals indicate closest equivalent rodent behavior/construct. Level of evidence indicated is for construct, not specific measure.
	Communication	Self-report survey, communication recording analysis, observational ratings	TBD	1	Fischer & Mosier (2014)	Some forms of survey, recording analysis, and observational ratings have been used in NASA analog environments (e.g., NEEMO, HERA). General methods have been used and studied extensively in extant literature.	Ultrasonic Vocalizations emitted during social interactions Response to vocalizations form conspecifics	Faure et al (2016) Scattoni et al (2011)						
							Deposition of social olfactory pheromones	Arakawa et al (2008) Wohr et al (2010) Crawley (2007)						Note: Level of evidence indicated is for construct, not specific measure.
	Bonding	Observational ratings, oxytocin	TBD	2	Cliff et al (2013)	Recommended measurement methods pulled from general literature and recommendations from researchers for this construct. Not currently measured/evaluated by BHP.	Pair Bonding	Gobrogge & Wang (2015) Johnson & Young (2015)						
							Observation, Grooming, Inter/Intra-Social Interactions Oxytocin/Vasopressin levels							Note: Currently not directly studied by BHP. Level of evidence indicated is for construct, not specific measure.
	Supporting and Backup Behaviors (Supporting)	Self-report survey, direct behavioral measures, observational ratings	TBD	1	Roma et al (2015) O'Leary et al (2012)	One form of self-report survey currently part of Behavioral Core Measures experiment, related alternative surveys and observational rating approaches used extensively in a wide variety of contexts including NASA spaceflight analogs. Behavioral measure completing development and expected to be delivered to BHP NLT Q1 FY17.	**HIGH Operant Conditiong**	Rabin et al (2002)	Rabin	Impact only at 200 cGy Fe	Prot/250: 400 cGy; Fe/1000: 100 & 200 cGy;		R/ Male Sprague Dawley: unknown	
								Rabin et al (2011)		Impact at 0.1 cGy	C/290: 5-150 cGy O/1000: 5-100cGy O/600: 0.10-25cGy Si/600: 10-200cGy Si/380: 0.5-100cGy Ti/1100: 10-100cGy Ti/500: 5-100 cGy	Behavior is dependent on striatum functionality.	R/ Male Sprague Dawley: 2	
								Rabin et al (2015b)		0.5 cGy	He/1000: 0.1-10 cGy		R/ male Sprague Dawley; 2	
								Rabin et al (2015c)	Rabin	Variable	Prot/1000: 25-200 cGy Prot/150: 25-100 cGy		R/ male Sprague Dawley; 2	
							MOD Taste Aversion	Rabin et al (1998)		Impact at 10 cGy. Dose dependent Taste Aversion learning	Fe/600:10, 50 & 100 cGy	Indicative of integrety of the area postrema and the chemoreceptor trigger zone, within the medulla oblongata.	Rodent Species and Age Not Stated	
							LOW Acoustic Startle	Haerich 2005	Nelson	Fe/1046: 500 cGy Si/585: 500 cGy	Fe/1046: 500 cGy Si/585: 500 cGy		M/C57BL/6: 1.5	
							LOW Emesis	Sanzari et al (2013)	Kennedy	100 cGy	Prot			Rats- no emesis response
							Avoidance	Allsop SA et al (2014)						Note: Parantheticals indicate closest equivalent rodent behavior/construct. Level of evidence indicated is for construct, not specific measure.

Key Indicators	Construct	Human Behavioral Measure	Level of Impairment	Level of Evidence	Relevant References	Deliverable Maturation	Level of Evidence Rodent Behavioral Measure (Bold Indicates Some CGR Data)	Relevant References	Active SRE PI's	Level of Impairment (Bold indicates PRA)	Dose Exposure (Ion/Energy (MeV/n))	Underlying Mechanism: CNS Effect	Time Scaling (Spp/ age of rodent at Irrad (mo))	Comments
Individual Behavioral States (e.g. mood, stress, anxiety/fear, separation/loneliness, frustration/boredom, motivation)	Stress	Visual Analog Scale				Currently part of Behavioral Core Measures experiment	Immobilization	Pitmann et al (1988) Ostroumov al, 2016				Corticosterol increases	R/Male Long Evans: 2	
	Depression	Beck Depression Inventory (BDI-II)			Beck (1972)	Currently part of Behavioral Core Measures experiment	Forced Swim Test	Castagné et al (2011)						
							Inescapable Shock	Wellman et al (2016)						
							LOW Sucrose Preference (Anhedonia)	Britten et al (2014)	Britten	None	Fe/1000: 20 cGy			
							Tail Suspension	Castagné et al (2011)						Hind-limb suspension studies. No reports?
							Social Defeat	Hollis et al (2014) Iniguez (2014)	Limoli, Eisch?					
							Leaned helplessness Novelty-Suppressed Feeding		Limoli, Eisch?					
	Mood	States - Short Form (POMS-SF) Zung Self-Rating Depression Scale Hamilton Rating Scale for Anxiety (HAM-A) Beck Scale for Suicide Ideation (BSS) and Beck Hopelessness Scale (BHS) Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) Psychological General Well-Being Index (PGWBI) Pittsburgh Sleep Quality Index (PSQI)			Zung (1965) Curran et al (1995) Hamilton (1959) Beck (1974) Beck (1988) Endicott (1993) Dupuy (1984) Buysse (1989)	Currently part of Behavioral Core Measures experiment	**HIGH Elevated Plus Maze**	Rabin et al (2015b)	Rabin	0.1 cGy	He/1000: 0.1-10 cGy		R/ male Sprague Dawley; 250g	
							HIGH Changing Reinforcement Schedules	Rabin et al (2011)	Rabin	Dose and Ion specific impacts on ability to deal with changing reinforcement schedules.	C/290: 5-150 cGy O/1000: 5-100 cGy 0/600: 0.10-25 cGy Si/600: 10-200 cGy Si/380: 0.5-100 cGy Ti/1100: 10-100 cGy Ti/500: 5-100 cGy	Depends on functionality of dopaminergic systems.	R/ Male Sprague Dawley: 2	
							HIGH Open Field Avoidance	Pecaut et al (2004)	Nelson	No Impact	Fe?1000: 10, 50 & 200 cGy		M/ Female C57BL/6 mice: 2.5	
	Anxiety						Light-Dark Exploration	Mineur et al (2006); Toth et al (2012)					Mice: 2	
							Light-Dark Exploration	Mineur et al (2006); Toth et al (2012)					Mice:2	
							Vogel Conflict Test	Crawley (2007) Blanchard et al (2003)						
							Marble Burying	Crawley (2007)						
							Unpredictable Chronic Mild Stress	Mineur et al (2006)					Mice:2	

Key Indicators	Construct	Human Behavioral Measure	Level of Impairment	Level of Evidence	Relevant References	Deliverable Maturation	Level of Evidence Rodent Behavioral Measure (**Bold** Indicates Some CGR Data)	Relevant References	Active Radiation PI's	Level of Impairment (Bold indicates PRA)	Dose Exposure (Ion/Energy (MeV/n))	Underlying Mechanism: CNS Effect	Time Scaling (Spp/ age of rodent at Irrad (mo))	Comments
Operational Task Performance (e.g. robotics, vehicle control, EVA, contingency scenarios, dual tasking)	Robotics Operation	ROBoT			http://nix.nasa.gov/search.jsp?R=20130012667&qs=N%3D4294916663	Currently part of Behavioral Core Measures experiment								
	Vehicle Control and EVA	MMSEV Flight Simulator				Currently in use in HERA								
Arousal and Regulatory (e.g. sleep, circadian phase)	Sleep duration	Actigraphy	TBD; general recommendation of 7-8 hours a night, but individual differences exist	1	Barger et al (2014)	Extensively validated as indirect measure sleep duration in ground studies and on ISS; high TRL/CRL. Less direct than EEG.	**LOW Actigraphy** Sleep island		Davis					
	Sleep architecture	EEG	TBD; persistent changes (e.g. reduction of) sleep stages	1	Dijk et al (2001)	EEG and PSG used extensively on the ground; small n of PSG	**LOW EEG**	Wellman et al (2016)	Britten (Prelim)				R/9	
	Circadian Phase (predicted)	Actigraphy	TBD	2	Flynn-Evans et al (2016)	Uses Jewitt model and actigraphy data to estimate whether circadian trough is at	**LOW Actigraphy**		Davis					
	Circadian Phase	6-sulphatoxymelatonin (aMT6s), collected every 2 to 8 hours over a 24- to 48-hour period	TBD	1	Benloucif et al (2008)	Extensively validated as estimate of melatonin production. Not used in flight yet, but will be incorporated in upcoming ISS study Lighting Effects. More direct than modeling.	SCN ephys Biochem markers							