2019 Human Research Program Standing Review Panel

Research Plan Review for:
Central Nervous System / Behavioral Medicine / Sensorimotor Integrated Research Plan

Final Report

I. Executive Summary and Overall Evaluation

Background for the review:
The Central Nervous System (CNS) / Behavioral Medicine (BMed) / Sensorimotor (SM) Standing Review Panel (SRP) recognized: a) the fully integrated research plan is a new approach to the Human Research Program (HRP) and that this is the first review panel where the disciplines (CNS, BMed, and SM) are reviewed simultaneously; b) the overall research plan has been formulated earlier in 2018 so that this was primarily a review of the overarching research approach; c) some of the questions in this review were written as "yes-no" answers but the panel interpreted that as opportunities to provide suggestions as to specific content and opportunities; d) the research into HRP is for the benefit of the health and wellbeing of the astronauts with the need for information that will inform the Operations of NASA in preparation for spaceflight, emphasizing the Mars mission (in this review) and that "go/no-go" decisions are based on the ability to avoid or mitigate risk and will be strongly impacted by the training and resilience of the crew; e) that research involves basic understanding of mechanisms but that the focus is on the application of the knowledge to space exploration, with the research done through grants and contracts that are designed or specified to address particular issues/questions; and f) the risks are avoided or mitigated by a range of solutions including engineering that not only requires many years to implement but is severely limited by both size and weight of material used in space missions, particularly challenging for a 3 year Mars mission, likely to be 2-3 decades in the future.

The SRP acknowledged the substantial effort that went into the development of the new integrated research format; the preparation, presentation and discussion of the NASA staff; and that reasonably frequent ongoing input from external advisors for both the integrated research program and the individual disciplines is essential due to the complexity of the issues and rapid progress in biological research. In the preparation of this report, an effort is made follow the outline and to reduce repetition. The SRP members appreciated the opportunity to assist NASA and its missions.

Overall evaluation:
The integrated approach among disciplines is strongly supported and ongoing research within the specific disciplines must frequently update the integrated plan to avoid any of the disciplines within an integrated program pursuing approaches that are no longer necessary. At the same time, it will be essential to continuously follow progress and breakthroughs in relevant areas of research to accelerate their assimilation for the goals of the program. At times, it may even be appropriate to steer such breakthroughs into areas directly or indirectly addressing topics of relevance. The Overall CBS Integrated Research Plan/Implementation Strategy (Presentation Slide 89) is complex and denotes a strong dependency on computational modeling. While such modeling will be useful for integrating a good deal of the scientific literature, the problems addressed in the Mars mission will not be informed by large data sets given the uniqueness of the deep space environment with the "high Z" particles, prolonged microgravity, unique social environment, significant lag-time required for interaction with mission control, and the inability of the research to reproduce the environment. Given the limits of a big data approach based on what is inherently a small n set of observations, one should carefully combine a nomothetic approach, which focuses on obtaining general rules for specific population and an idiographic approach, which focuses on specific individual-based decision situations. Among the nomothetic approaches, decision trees offer some

advantages over other machine learning tools because they codify specific decision variables that minimize future risks.

This is fully compatible with current "Clinical Decision Support" for healthcare. The Overall Implementation Portfolio Schedule includes 6 areas of Research Emphasis and extends to FY 31. Information, knowledge, technology, and mission timeline may dramatically change in that time. The research questions and objectives should be clearly reviewed and defined over reasonable increments, such as 4-5 years, timelines that are generally appropriate for research grants. It is recognized that the goals of NASA may change based on the policy of the extant administration, however, with the current inevitability of deep space exploration and the competition/collaboration among nations, the *human research for deep space missions must be sustained* given the need for continuity in research and the predictable loss of progress from starting and stopping essential research themes.

Astronaut performance will be based on serial selection criteria (decision-tree with various gates). With the complexity of human biology and the genetic–to-phenotypic performance dependent on the life-long environment and resilience, using a "precision medicine" approach to selection will be difficult. Nonetheless, both obvious traits such as gender and certain genetic predispositions that can be defined (e.g., possibly DNA damage response or cellular response to the deep space radiation environment) would be reasonable to take into consideration, recognizing that precision medicine has shown that most medical conditions are based on a relatively large number of multiple minor-impact factors. Emerging knowledge of brain development and function, such as the module-and-node models of brain function and the ability to monitor brain functional capacity, to some extent, by functional magnetic resonance imaging (MRI) and electroencephalogram (EEG) provides a significant impact on which to map CBS effects. The long-term (years- decades) biological effect of the space radiation on individual cells and tissues is not necessarily predictable from short and medium term (years) data and such experiments are difficult to do. Therefore, new concepts should be developed informed by the ongoing revolution in our understanding of the molecular processes underpinning the response of cells to ionizing radiation – particularly high-Z particles. That the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratories (BNL) is now operational will allow for improved assessment of cell fate given the likelihood of multiple "hits" to a cell from different particles. Although it may take years to understand the underlying mechanisms and the potential for cell recovery, such knowledge will be essential for the informed quantification of permanent injury that might lead to radiation-induced cell death or cancer, particularly in stem cells. At the same time this knowledge is likely to inform approaches for countermeasures. It is important to point out in this context that this reasoning applies to tissues beyond CBS and is therefore worth defining.

Defining the specific experiments will require thorough analysis of results obtained, however, clearly defining the research conditions and procedures is critical to be able to combine or compare results from different laboratories. The experiments should focus on the likely conditions encountered and the somewhat empirical use of medical countermeasures, however, some degree of bracketing the conditions with higher albeit unlikely conditions to be encountered can provide important knowledge of mechanisms of damage and recovery. It is critical for the program directors to examine ongoing programs frequently to avoid blind alleys. On the other hand, when there are proposed mechanisms of action such as inflammation, studies using existing anti-inflammatory agents should be evaluated early on to help guide mechanistic and countermeasure research.

The Performance Outcome Level (POL) will be influenced by the interpersonal properties of the team. The psychological impacts of space travel and team effects on individual and group outcome as investigated in the human exploration research analog (HERA) will be critical. The individual functional assays as have been done by the astronauts in space and on return to Earth and the time course for resolution of functional decline will be useful for assessing POLs. Recognizing that Central Nervous System (CNS) and sensorimotor (SM) functions are interactive makes it important to have diagnostic tools available during the Mars mission (e.g., EEG or variants, or other imaging tests). These will be among the useful biomarkers that will likely include blood tests (very low volume "chip assays") and other activity/attitude measures available with monitoring devices. Biomarkers are best understood with serial measurements; a single time point may not predict outcome. Ongoing biomarker and radiation mitigation research for whole body exposure being conducted by National Institute of Allergy and Infectious Diseases (NIAID), Biomedical Advanced Research and Development Authority (BARDA) and Department of Defense (DoD) can help inform NASA, and communication with these agencies is essential.

Since many of the issues are related to absence of gravity, engineering strategies to provide exposure to artificial gravity for the appropriate amount (0.4G proposed) and time might mitigate or prevent many of the anticipated problems. Recognizing from the discussion that this has been considered in the past, this may be a reasonable time to reopen the discussion given the long duration of the Mars mission and the requirement to change gravity and function promptly upon attaining a Mars landing.

II. Review of the Research Plan for the Central Nervous System (CNS) / Behavioral Medicine (BMed) / Sensorimotor (SM) Integrated Research Plan

1. a) Assess if the CBS Integrated Research Plan represents a transdisciplinary approach that fully integrates the three CBS (CNS, BMed, and SM) disciplinary approaches with respect to the spaceflight environment (which includes, but is not limited to: space radiation, altered gravity, isolation and confinement, that may synergistically interact to increase risk to a crew by negatively impacting their health and performance)

- The SRP strongly endorses an integrated research approach. It is critical to review progress in the individual disciplines and their integration sufficiently frequently and with sufficient expertise. These need not be overly formal reviews but rather updates to incorporate new findings, methods and interactions, and avoid extending work in areas that end up being less relevant to the integrated solution as research results accrue.
- The importance of behavioral processes and interpersonal relationships as investigated by HERA should be emphasized more. That results of psychological research are harder to convey is understood, however, this was felt to be the weakest part of the program as presented. Given that selection process and resilience of astronauts is extraordinary, it is likely that there are options to train the way out of failure as a form of countermeasure.
- Given the focus of the research is ultimately on operational performance, it is critical to more clearly define endpoints and integrate endpoints with mission deadlines. While a Mars mission is the focus, other space explorations are considered so that intermediate steps for longer-term missions must be clearly defined as they can be assessed in shorter-term missions (i.e., identify 4 years. vs 20 years. questions). Where decisions are go/no-go, using a decision tree may ultimately be the approach by which to support/direct research and assemble results. Moving forward, deliverables need to be clearly defined and classified as research- and task-oriented programs. This may mean that mechanistic studies are less important than maximizing the use of data available to reach an operational standard. Furthermore, attempting to estimate overall risk to human health for a mission is difficult in that the data sets are limited in size and error bars for risk estimates are large.

While risk estimates are used in policy, a decision-tree approach is more practical for operational decisions.

- The panel recommends development of a plan to assure overall data collection and management. If those who need the data cannot go back and access it, then the usefulness is too limited. Access to fundamental data leads to firm conclusions.
- Highly successful astronauts might help establish benchmarks for performance.

b) Assess how well the CBS Integrated Research Plan provides strategies to characterize and mitigate the three related risks via countermeasures.

- A precision medicine approach would break this into dozens of interacting issues. The emphasis on precision medicine may be overdone given the limited data set to determine POLs and permissible exposure levels (PELs) and the limited applicability of precision medicine to date.
- A question to consider is how to attack CBS integrated effects in a general way (e.g., artificial gravity solves much of microgravity effects). If radiation reduces efficacy of recovery mechanisms, prevent both insults as much as possible. Artificial gravity does not have to be 1 G, 0.4 G may be sufficient (Harris *et al.*, PLoS One, 2014).
- A more strategic approach to countermeasure development is needed. The specifics of the computational approach (Slides 74-78 pf the Presentation) are unclear. It is helpful to identify large classes of countermeasures (e.g., nutritional, pharmaceutical, nutraceutical, behavioral) and to test some empirically before extensive investment in mechanisms, (e.g., anti-inflammatory agents).
- Increase liaison between scientists working on doing radiation countermeasures for other areas, such as nuclear/radiological emergencies (BARDA, NIAID).

2. Does the rationale and evidence provided in the review materials support the scientific approach to characterize and mitigate the CBS risks?

   - Yes, in general, recognizing that this is a nascent research plan. The Problem Statement summarized the problem at a fairly high level with the data available from the different disciplines (C, B, S) not discussed in detail. The CBS Integrated Research Plan/Implementation Strategy (Slide 89 of the Presentation) included a reasonable range of categories (various boxes). As noted, the dependence on big data and unspecified computational modeling may not be very productive given the uniqueness of the problem for prolonged spaceflight on a Mars mission.
   - Studying the interaction of risks is critical, as recognized in the adaptation of an integrated research plan. For example, social interaction can be tested along with another insult. Single discipline data should be studied further, particularly long-term data available from studies such as non-Human primates (NHP) survivors from other research. This will provide some very long-term (many year) data on radiation effects including effects on cognition and aging. The NHP long-term survivor cohort at Wake Forest is a good example. Anatomical and biological (gene expression) data could be made available for brain tissues. While these are all photons and no high Z particles, which creates different

cellular damage worth studying, there are a range of whole-body doses that can help define radiation effects on neural tissue (see Andrews *et al.*, 2017, 2018, 2019).

- GTEx (Genotype Tissue Expression Project) – This national resource provides tissue-specific gene expression profiles for normal human subjects. This data base can provide observed differences between sexes provide a baseline for healthy individuals. This could be used to compare returning astronauts to baseline and provide explanation/interpretation to existing data from astronauts. Growing numbers of studies include genomic data that could be leveraged. Good controls are critical to most experiments and often the most difficult part of them.
- The complexity of the data from each of the disciplines and the need to understand combined effects should include grantees and other outside expertise where possible. Input from program is essential to enable research to be directed when appropriate and necessary. Functioning like cooperative agreements (NIH U01) grants with involvement of program officers facilitates integration.

3. Is the overarching research strategy (as represented in logic models and the sequence of research tasks and milestones) presented in the CBS Integrated Research Plan sufficient to characterize and mitigate the CBS risks?

   Reformulate question: What aspect of the overarching research strategy (as represented in logic models and the sequence of research tasks and milestones) presented in the CBS Integrated Research Plan is sufficient to characterize and mitigate the CBS risks?

   - This early in the program and with the complexity of the individual disciplines much less their interaction there are many unknown unknowns. Program leadership needs to circle back to these questions periodically to incorporate new data. The panel recommends every 2 years.
   - A Fast-fail strategy is more advantageous for narrowing applicable science. Many countermeasures will fail, and this can be checked quickly. This needs to be emphasized rather than sustain basic science into areas that are shown to not be promising, recognizing that every basic science grant will argue applicability to countermeasures.
   - Ongoing research by the Translational Research Institute for Space Health (TRISH) was not examined or reviewed. Leverage the TRISH portfolio for datamining. The HRP elements studied by TRISH need to be considered and directed as necessary by NASA including input from the Office of the Chief Health and Medical Officer (OCHMO).
   - Recognized in the discussion with NASA staff: Managing the chart (CBS Integrated Research Plan/Implementation Strategy, slide 89) is very complex, such that an operator must check that the arrows are followed, and links are acknowledged at multiple levels. This includes identifying specific people responsible for different stages including handoffs when people leave (retirement, resignation, transfer, etc.) which is certain given the timeline extending to FY 31. Documentation is extensive and necessary for effective management of this large-scale effort.
   - Ultimately, HRP-generated experimental information is necessary for operational decision-making. Consider both operational implementation and occasional collaborative exercises between HRP and Operations for understanding how the information will actually be used and to help ensure the charts and strategies are relevant and useful.

- Regular meetings of program leadership and NASA-funded scientists are necessary for communicating results and modifying strategic direction. The overarching plan (CBS Integrated Research Plan/Implementation Strategy, slide 89) is a living document, so an annual iterative process with ad hoc interventions by program administrators would be necessary to refine and, in some cases, end unproductive avenues of research.

4. The review materials document the following research areas and techniques. Are the research techniques and the strategy for their use, presented in the CBS Integrated Research Plan, appropriate for identifying impacts to human health and performance in support of spaceflight exploration and developing countermeasures?

   a. Translation of animal results to humans

- More studies are needed using NHP data, whether studies are done by NASA or others. NHP brain characteristics are fundamentally different from those of rodents and much more similar to humans. In primates, the white matter (indicating connectivity) comprises a higher proportion of the brain volume (~40% versus ~10% in rodents). Interconnections between brain regions distinguish primates (including humans) from rodents.
- The Wake Forest Radiation Survivor Cohort hosts long-term studies of irradiated animals (1-8.5 Gy, not high-Z, however); this resource should be leveraged.
- The CBS program needs to understand the relationship between phenotypes in humans and rodents. Cellular damage likely involves conserved mechanisms, but organismal function is more difficult to model. Defining phenotypes for different species is critical.
- The program should seek to understand phenotypes in terms of how they affect the validity of human translation. Blood pressure is an example of where such differences exist between species at an organism level.
- Treatments need to be standardized, especially for difficult-to-quantify effectors.
- Countermeasures must consider differences in microbiome, metabolism, etc. if implemented in animals.
- As possible, strictly define control conditions for future studies. Standardize control conditions sufficiently and include controls in experiments by different labs to enhance comparison of data.
- A challenge is that given the timeline, there is little room for mistakes and confounding of batch analysis with differences.
- Understanding orthologous relationships between species and between different mouse strains is important. Jackson Labs works hard at this and can help; outreach and use of their expertise is recommended.
- The Cambridge Neuropsychological Test Automated Battery (CANTAB) was explicitly developed to examine cognitive constructs translationally. Thus, the dysfunctions observed in rodents can be examine with the same tests to determine whether the same dysfunctions can be seen in humans. This platform is recommended.
- Cage size is a variable for exploration; This can be considered an analogous environmental variable to the crowded condition in space.

- There are many reasons to be cautious when extrapolating from studies of rodent social behavior to humans.
- Isolation paradigms exist for rodents. However, species differences must be considered. For example, the mice do better alone and tend to fight when placed in groups, but rats are more social and become stressed and behaviorally abnormal when housed alone. Programmatic planning and project reviews need to keep in mind the best rodent model to use.
- Isolation is not a good term for what is going on in a spacecraft. Humans are susceptible to global deprivation rather than true isolation, which is the implementation strategy in rodents. Humans may be socially disconnected, but not truly isolated during space missions.
- Evidence on gender differences is described. Age range needs a similar approach. The risks and outcomes may have age-related effects. The rodent ages studied need to model the closest approximation of astronaut age; the CBS is aware that this is currently not the case, rodents are much younger on a relative life scale, and at that young age are more likely to have neuronal proliferation/repair, as compared to less regeneration in adults.

b. Data-mining efforts in biomarkers relevant to these risks (more on specific biomarkers in "4.e")

- The panel interpreted this term as datamining of *markers from the literature*. The data-mining term, used often, does not speak to the level or rigor involved. Weight of evidence assessments should take into consideration the level of rigor and reproducibility; quality of the work should be a weighting factor.
- We encourage the effort to move investigational lab biomarkers to practical spaceflight applications. Such studies may be difficult to implement, and may produce contradictory results (endpoint differences, batch effects, etc.).
- Biomarker studies must be reproducible. The same data and the same software (for algorithms) should be able to be applied by anyone to produce the same output.
- To use biomarkers when making predictions in humans requires a higher level of scrutiny than lab use.
- Data and underlying software code must be open source and available.
- Human Subjects Protection issues need to be resolved.
- Biomarkers must be robust. Independent data sets should be replicable for individual biomarkers.
- The analytic approaches taken should avoid overfitting limited data.
- Combined assessment of multiple biomarkers is suggested.
- Validation of biomarkers in a clinical trial would be ideal but this is probably not feasible, so the CBS plan should incorporate independent validation of biomarkers, using an investigator/lab independent of the initial investigator to validate. The program should be clear that this is not an indictment of original PI, but rather a requirement for a higher standard of validation.

- There is a need for a repository for raw data on biomarkers. Existing databases such as the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov) or the European Bioinformatics Institute (EBI) (https://www.ebi.ac.uk) and other public databases should be leveraged.
- Analytic strategies and code used for analysis of biomarkers should be publicly available for scrutiny and use by multiple labs; the panel recommends use of GitHub (https://github.com). Before moving the use of biomarkers to operations, code review and validation should be performed.

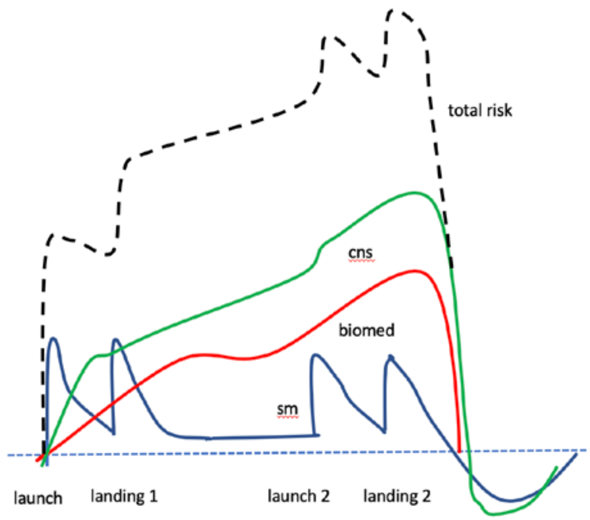
c. Identification of common brain performance pathways

- Performance in one area may not be correlated with performance elsewhere. For example, working memory effects may not correlate with reaction times. Diseases exist where some performance outcomes are affected much more than others. Assumption of common brain performance pathways needs to be thoroughly examined. There is likely to be more than one test needed to develop an integrated measure of performance. This is confirmed in the provided materials but should be emphasized.
- New approaches such as Neurite Orientation Dispersion and Density Imaging (NODDI) and modular approaches to brain interconnectivity should be explored (e.g. Farhani *et al.*, 2019; Hilger *et al.*, 2017).
- The program needs to define pathways of interest (salience, executive control, default mode). Measures can be further parsed. Network-level correlative approaches are encouraged, for example approaches such as those used by the Bassett lab at the University of Pennsylvania (see Sizemore *et al.*, 2019).

d. Operational performance domains

- Awareness exists in the literature of the severity of the problem, especially with SM.
- Operational assessments have been better defined for the transition to space, and less so upon landing for SM. Currently it is clear that astronauts need assistance with adaptation to post-flight SM impairment, and in the setting of a long mission and landing on Mars with its 0.38 G this problem will be greater; this problem should be addressed.
- A portfolio imbalance is evident in the plan. Data presented show a paucity of SM studies early in the plan; given the known importance of this element of the CBS integration, more work should be done in this domain to avoid the risk of having to repeat studies later.
- Consideration should be given to possible sex differences in how the various risks and their interactions might affect males and females differently (as described in the 2011 NASA Decadal Survey, "Recapturing a Future for Space Exploration: Life and Physical Sciences for a New Era"). Previous research has addressed much, but presently may require additional attention.
- The synergistic effect curve on Slide 95 seems to underestimate the peaks in SM effects and the effect on total risk. Need to consider if recovery is the same as expected for SM.

The total risk may be greater, for example:



(drawing by panel member Dr. Laurence Harris)

- The only venue for true experimental confirmation of synergistic effects is space. Projects on the International Space Station (ISS) that can address this should be given priority.

e. Identification and monitoring of actionable biomarkers

- The panel recommends study of performance surrogates in spaceflight and seeking feedback on what can actually be measured in space.
- The panel recommends framing this question to include operational biomarkers in addition to blood- or laboratory-based biomarkers.
- Imaging (video monitoring) "biomarkers" of crew behavior and other assessments of individual's performance may be useful. We recognize that crew member privacy must be respected, but this is an untapped data stream.
- Validation is essential; the panel recommends seeking further guidance on appropriate studies.

For blood-based radiation biomarkers the following apply:

- BARDA and NIAID have spent a lot of time on this already for whole body exposure. The panel recommends outreach to these groups in order to leverage existing information.
- Although BARDA and NIAID work does not include particle exposures, some principles may be similar enough to build on x-ray and neutron work.
- Some newer markers may be better conserved across species (for example microRNAs), when compared to protein biomarkers. Cross-validation is required.
- Interspecies work from mice to guinea pigs to NHP to humans can provide positive and negative controls.

- Some analytes routinely acquired (e.g., in a typical clinical pathology panel) do not change in the context of anticipated CBS exposures, and so can be used as a benchmark against which to compare more radiation- or stress-responsive outcomes. Look at all markers across the board and use a computer-generated decision tree to estimate dose. Also, single time points may be misleading; look for patterns over time.
- Studies of the effects of microbeams are useful for looking at effects on single cells and allow the study of the effects of high Z particles (e.g., Columbia microbeam irradiator).
- Proton research should be of interest for CBS. Many medical centers do this so some biomarkers may possibly be used to assess high focal linear energy transfer (LET) exposures through experimental use of the Bragg peak effect, as a model of high-LET GCR exposure.

f. Computational modeling

- The term is vague as presented. The CBS program needs to carefully define the modeling in context. Laboratory studies use modeling to develop hypotheses or countermeasures. The type of model varies widely according to the data and question being asked.
- It seems at the moment that there is a lot of data and something needs to be done with it; funding for review and analysis of extant datasets is recommended.
- Modelling approaches should go beyond categorization and data management, to seek conclusions that have real-world applicability.
- In-flight computational models are more akin to clinical support. Machine learning tools might be useful. Image recognition may be useful.
- The approach needs to be more specific in model types. Defining end goal of models (use cases) will help. Then work backwards to identify what is appropriate to reach those goals. Overly optimistic interpretation of what computational models can tell the program.
- Ensure integrity of methods. Make all code available publicly.
- Idiographic and nomothetic approaches should both be considered. The idiographic emphasizes the subjective and unique experience of an individual, whereas the nomothetic approach studies the numerical and statistical side to draw universal conclusions. There are different experimental designs that are aimed to examine nomothetic versus idiographic aspects. In particular, n of 1 studies have been conducted to examine individually specific factors (Lillie *et al.*, 2011).
- For statistical learning models, generally one needs large numbers. Numbers will always be limited for CBS, even with external validations outside of NASA (usually only 20-50 people). The CBS should stay grounded in what computational models may be able to accomplish for future planning. There is now evidence from several large-scale behavioral studies such as the UK Biobank, the Adolescent Behavior Cognitive Development Study, and the Human Connectome Project that behavioral models generated by different biological variables only account for a small percent of the observed variance (typically around 10%). This means that computational models will not be sufficiently specific to make individual level predictions and are therefore not useful for making go/no-go decisions. It will be important to shape the expectation as to what the precision of any computational model predicting behavior (or decision-making) can be at this point in time.

- For additional perspective on sample size and effects predictions, see Paulus and Thompson, 2019; and Funder and Ozer, 2019.
- Image data may help (analysis of existing video which may allow analysis of affect and task performance data). Simulations may be helpful, and an abundance of video data concerning participant interaction is at hand. HERA, for example, has already provided an enormous amount of data. Need to leverage the massive datasets for small cohorts.
- Given the low numbers of individuals available for study, longitudinal n-of-1 studies may be of value.

g. Development/adaptation of CBS Integrated Research Plan risk-based Performance Outcome Levels (POLs) and Permissible Exposure Limits (PELs).

- The panel affirms the value of the key parameters being studied, but since they are highly variable, how can they be quantitatively assessed for a combined insult? POLs and PELs seem loosely defined within the integrated program. Their importance in controlling the mission is understood but the details will obviously be critical.
- The CBS program and other groups within the NASA framework have some control over the definition of expected performance outcome levels. How do these POLs and PELs interact for different risks in CBS?
- The panel suggests more detail is needed regarding the POL parameters in the context of combined CB&S insults. What elements of performance are most critical? What are the thresholds for concern? The panel suggests developing item banks to make up scale including granular elements defining a POL, for example the use of psychomotor vigilance tasks (PVT).
- The panel recommends that the CBS cannot rely solely on computational models for determination of POL and PEL limits, since these are generally expressed as independent maxima and minima which will almost certainly shift unpredictably when the risks are considered together.
- Different effects from various CBS risks are on different timescales (recovery may be also). Considerations of temporal relationships need to be incorporated.

h. Countermeasure development

- The panel notes that countermeasures to address specific brain states are not evident and recognizes this is early in the process.
- Inflammation is likely to be a relatively easy target for the development of countermeasures, and also may serve as a broad biomarker for multiple domains of impairment across the CBS integrative approach. We recommend that some empirical studies using anti-inflammatories may speed up assessment and mitigation strategies.
- Artificial gravity or additional visual or tactile cues to gravity/orientation are fields of interest.
- Training should be considered a countermeasure. Artificial gravity would be providing training for expected gravity levels on Mars.

- Countermeasure development seems to start in 2021; the panel recommends that empirical research should start sooner.
- A detailed literature review is recommended to know state of the art for countermeasures in this realm; the review materials presented from 2016 were very helpful and informative, but should be updated.
- Nutritional supplements and antioxidants need to be better defined/organized. Classes of supplements or treatments should be defined (growth factors, cytokines, etc.).
- Newer therapies (e.g., cellular based) should be considered.
- For confinement, a reasonable countermeasure might be supplying a virtual reality (VR) simulation of freedom. Such an intervention might work well, by providing a break. But VR might also be frustrating as astronauts re-emerge and face their prevailing reality, which does inevitably include confinement. Cycling between virtual freedom and actual confinement may produce unexpected effects, and having some basis to answer that question would be worthwhile.
- An alternative approach would be to study how individuals accept confinement and come to terms with it, perhaps drawing on literatures regarding how people come to terms with adverse situations like confinement to bed, etc.
- The approaches of the Military Suicide Research Consortium should be considered (https://msrc.fsu.edu), particularly studies ongoing on reconnection. Principles of facilitating personal connections to family and social support mechanisms are of demonstrated value and will likely be of benefit in the setting of prolonged exploration missions.
- Cognitive/Vestibular interactions should be explored. The vestibular system influences the perception of "body ownership" and self, and this is an area of active research (Harris and Ferrè, 2017). Using electrical signals (galvanic vestibular stimulation: GVS), one can temporarily deactivate the vestibular signal and study its effects on the sense of body ownership. Removal of gravity and the effects of such treatment on self-identity may be of interest.
- Neuromodulation techniques are worth exploring, including transcranial magnetic stimulation (TMS) which produces neuronal firing, transcranial direct current stimulation (tDCS) which increases neuronal excitability (Nitschke and Paulus, 2001), and transcranial alternating current stimulation (tACS). These, if precisely applied, can stimulate specific parts of the brain and have anti-depressive effects. This is a rapidly developing field, with developing standards of safety (Bikson *et al.*, 2016), rigor and reproducibility (Bikson *et al.*, 2018).
- Although study of primate brain effects using high-Z exposures is difficult currently, archival materials may exist for which post-hoc pathologic studies may be possible.
- The panel recommends that the CBS consider the possibility of studying proton (and other ion) therapy patients for these combined risks. Meta-analysis may be useful.
- The panel recommends seeking autopsies to study the brains of astronauts who have traveled beyond low-earth orbit. A useful model could be the brain banks maintained by the national Alzheimer Disease Research Centers and other entities studying other brain diseases. These Centers have developed strategies for advance assessment, planning, acquisition, and study of brain effects after death (e.g. Munoz *et al.*, 2019).

5. Are the anticipated final deliverables (research products, end-state or final outcomes) appropriate and feasible to identify impacts to human health and performance in spaceflight?

    - The panel suggests additional clarity on what the intended deliverables are. Final deliverables (better termed ‘applicable deliverables’?) may not be possible in the context of the need for interim outcomes. An iterative approach is needed, in order to be responsive to long-term needs while remaining flexible for short-term opportunities.
    - The panel suggests listing intermediate deliverables and milestones. A better description of checkpoints and when to give up pursuit of a particular approach is needed.
    - Some other threats outside the domain of the CBS integrative program are likely to also affect the risks under study. Therefore, it is critical to interface with other parts of program early on (e.g., cardiovascular/vestibular overlap, cardiovascular/CNS overlap).
    - Even in the presentation, it was not clear that deliverables are concrete enough to be appropriate and feasible. Moving to a decision tree based, flexible strategy is recommended.
    - The practicality of deliverables should be kept in mind. There is a separation between research goals and implementation that needs to be acknowledged.

6. Please comment on any important issues that are not covered in above, that the SRP would like to bring to the attention of the HRP Chief Scientist and/or the Elements.

    - Radiation effects on cognition and SM are relatively well-defined, but the panel recommends additional work regarding interactive effects of social/psychological influences and team dynamics, for example effects of (and on) aggressive/disruptive behavior.
    - Also, with respect to behavioral outcomes: Are there behavioral endpoints that would terminate a mission? What is the solution for complete dysfunction in personnel? What is the protocol for dealing with extreme behavior? This may be an area of interest and need, considering the likely cumulative effects of multiple risks and the uniqueness of a trip to Mars.
    - Need full autopsies of the brains of astronauts that have traveled beyond low-earth orbit (LEO) to understand documented changes in spaceflight.
    - Need to request permission from individuals and family early on to arrange as much data collection as the program can get after death or incapacitation of an astronaut. Approach should be formalized and justified.
    - May be able to incorporate comparison to other brain tissue insults due to radiation (e.g., medical).

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