Topical: Reverse Translation Strategies to Support Cognitive and Behavioral Risk Characterization

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Abstract: A coordinated suite of measurements to assess humans and animals needs to be established to support the translation and harmonization of animal research data to the astronaut corps due to the necessity of using animal subjects for radiation testing. The identification of POLs and PELs for spaceflight stressors (i.e. space radiation, altered gravity, isolation and confinement, sleep disruption) individually and combined will depend on defining scaling factors or transfer functions that can be used to relate human and animal outcomes.

A critical issue for managing crew health for long-duration missions is how spaceflight hazards might impact cognitive and behavioral performance[1]. Due to the unique spaceflight environment, both human and animal research is used to characterize the risk of adverse cognitive or behavioral conditions that could affecting crew health and performance during spaceflight.

The need for translational approaches for crew cogitative and behavioral health and performance is twofold. First, animal data from radiation experiments requires translation to the human scale to understand if findings are relevant to the astronaut corps. Homologous behavioral tests in animals and humans have been identified and vetted for their ability to predict effects of drugs, emulate features of neurological disease, engage corresponding brain regions and circuits, and physiological mechanisms[2–4] and many are currently in use for radiation and other spaceflight stressor evaluation (*e.g.* psychomotor vigilance)[5]. The use of complementary functional imaging and electrophysiological techniques with behavioral tests would provide an independent assessment of the construct validity. Second, a robust approach needs to be developed to assess combined spaceflight hazards and understand the impact of spaceflight holistically.

Relevant to both challenges is the establishment of permissible outcome levels (POLs) which define acceptable levels of decrement for measures that correspond to outcomes relevant to either in-mission performance or long-term health [6]. The definition of POLs requires outcome metrics that can be adequately monitored to assess performance and provide triggers for initiating mitigation strategies. Once POLs are established the individual and combined environmental permissible exposure levels (PELs) that correspond to the defined POLs can be investigated in experimental studies.

For a reference mission to Mars, over 1,125 operational tasks and subtasks have been identified[7] and linked to component cognitive, affect, and social behavioral domains[8], Figure 1. These component domains can be assessed by direct observation, or by quantitative behavioral test batteries that evaluate surrogate outcome measures (*e.g.* "Cognition" battery)[9]. Surrogate exposures for flight hazards such as head-down bedrest, sleep disruption, and long-term confinement and isolation in ground-based facilities can be leveraged to assess changes in many of these domains directly in humans. However, characterizing the impact of space-like radiation exposure relies on animal experimentation guided by human epidemiological findings of the atomic bomb survivors, radiation therapy patients, and occupationally exposed cohorts[10].

Recommended CBS Operational Performance Measure	RDoC Mapping		LDSE Relevancy					Assessment Criteria and Ratings									
			Mission Tasks		BHP Competencies												
	Domain	Construct	Universal	Specific	Mission	Social	Personal	Construct Validity	Predictive Validity	Reliability	Sensitivity	ACTUAL Op Feas	ACTUAL Op Accept	PREDICT Op Feas	PREDICT Op Accept	Animal Analog	Animal Analog Rating
Longitudinal Actigraphy	Arousal and Regulatory Systems	Circadian Rhythms	N	Y	N	N	N	Med	Med	Med	High	Med	Med	Med	Med	Y	Med
Psychomotor Vigilance Test (PVT)		Arousal	Y	N	N	N	N	High	High	High	High	High	Med	High	Med	Y	High
Stop-Signal Reaction Time	Sensorimotor Systems	Motor Actions: Inhibition and Termination	Y	N	N	N	N	High	High	High	Med	Unknown	Unknown	High	Med	Y	High
Delayed Match-to-Non-Sample	Cognitive Systems	Working Memory: Active Maintenance/ Limited Capacity	Y	N	N	N	N	High	High	High	Unknown	High	Med	High	Med	Y	High
Delayed Match-to-Sample			Y	N	N	N	N	High	High	High	Unknown	High	Med	High	Med	Y	High
Effort Expenditure for Reward Task (EEfRT)	Positive Valence	Reward Valuation	N	N	N	N	Y	High	High	Med	High	Unknown	Unknown	High	Low	Y	High
Penn Emotion Recognition (ER-40)	Social Processes	Social Communication	N	Y	N	Y	N	High	Unknown	High	Unknown	High	Unknown	High	Med	Y	Med

Figure 1. Recommended core operational performance measures based on several criteria including Research Domain Criteria (RDoC) mapping, long-duration space exploration (LSDE) relevancy and animal analog equivalency.

There is now a critical need to establish a coordinated suite of measurements for humans and animals to define scaling factors or transfer functions for spaceflight exposure profiles. For example, periods of sleep disruption can be used to identify exposure limits in humans that elicit unacceptable cognitive impairment as is done by the Department of Transportation for airline pilots, train engineers, and truck drivers[11]. Animal cognitive performance in corresponding assays after sleep disruption can also be quantified and related to human performance by comparing standard effect size scores (*e.g.* Z-scores[12]). The relationship between human exposure-responses and animal homolog exposure-responses based on sleep as the stressor could be used as a scaling factor or transfer function for other exposure types relevant to spaceflight that cannot be assessed in humans. Animals can similarly be exposed to space-like radiation from the NASA Space Radiation Laboratory[13] across a range of dose profiles and the level of impairment compared to the impairment produced by sleep disruption. Mapping the animal radiation-to-sleep relations and the animal-to-human sleep relations for the homologous outcome measures allows extrapolation of a PEL for radiation in animals to humans at the POL and equivalent operational impairment level, see Figure 2. By extension, other human compatible stressors effects can be related to equivalent radiation exposure levels using animal response intermediates. Once individual stressor PELs are established, combined stressor exposure regimens could be used to estimate exposure limits corresponding to different mission scenarios.

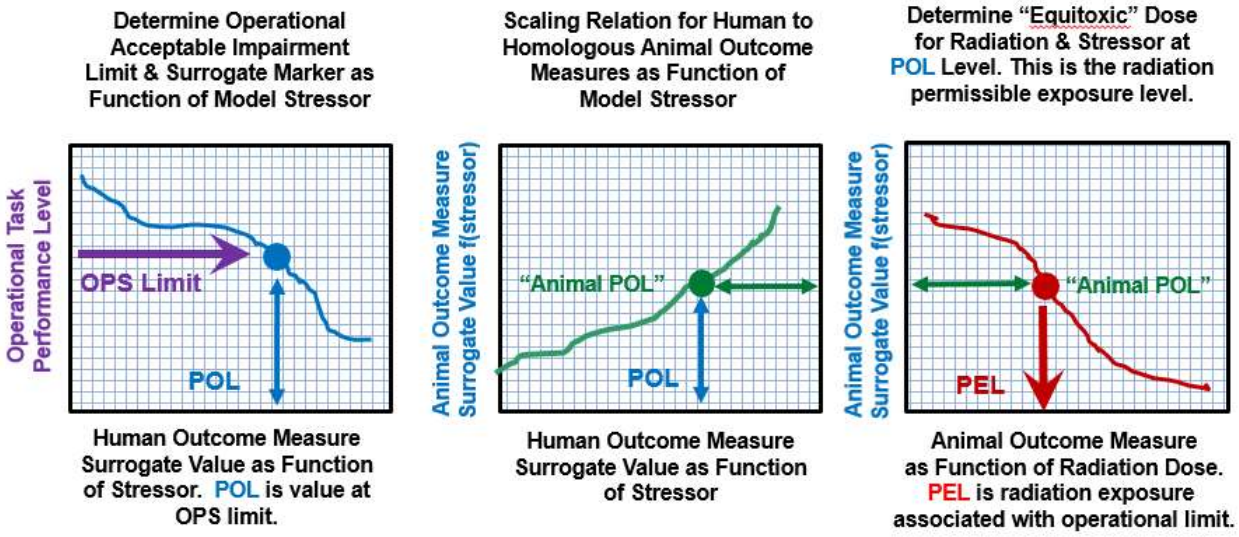

Figure 2. Effect Size versus exposure levels for setting POLs and PELs using animal intermediates and surrogate measures or biomarkers.

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