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Assessment of Spaceflight Medical Conditions' and Treatments' Potential Impacts on Behavioral Health and Performance

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ABSTRACT

Long-duration space exploration missions will pose significant risks to the physical and behavioral health and performance of the crew. We documented the presence and frequency of (1) behavioral health and performance (BHP)-relevant symptoms for each condition in NASA's Exploration Medical Conditions List (EMCL), (2) the BHP-relevant effects of applicable medical treatments in the current International Space Station (ISS) On-Orbit Medication List, (3) the breadth of potential BHP impacts of spaceflight medical treatments, and (4) the likelihood of adverse BHP effects of treating spaceflight medical conditions. BHP symptoms and effects were categorized by the six neurobehavioral domains of the National Institute of Mental Health's Research Domain Criteria (RDoC) framework. Including the cognitive effects of acute and chronic pain (e.g., attention, memory), 94% of spaceflight medical conditions include symptoms relevant to Cognitive Systems (e.g., attention deficits, confusion, psychosis), 36% include symptoms relevant to Negative Valence Systems (e.g., anxiety), 32% include symptoms relevant to Arousal and Regulatory Systems (e.g., sleep disturbances), 22% include symptoms relevant to Sensorimotor Systems (e.g., dizziness), 19% include symptoms relevant to Positive Valence Systems (e.g., mania), and 11% include symptoms relevant to Social Processes (e.g., social withdrawal). Only 2% of spaceflight medical conditions have no documented BHP symptoms. Of the spaceflight medical treatments, 63% affect Arousal and Regulatory Systems, 60% affect Sensorimotor Systems, 59% affect Cognitive Systems, 53% affect Negative Valence Systems, 38% affect Positive Valence Systems, and 31% affect Social Processes. The breadth of potential BHP impacts was bimodal, in that 27% of spaceflight medical treatments had no documented BHP effects; however, 27% of treatments may produce adverse effects across all six neurobehavioral domains. Historical prevalence data on medical conditions, symptoms, and complaints from 14 years of International Space Station operations coupled with documented BHP effects of recommended treatments indicates the potential for up to 481 adverse BHP effects of spaceflight medical treatments per person-year. Assessing the potential BHP impacts of spaceflight medical conditions and their treatments highlights the interactive nature of operational risks, and can provide an enhanced evidence base to support integrated research and countermeasure development strategies for long-duration exploration missions.

1. INTRODUCTION

Long-duration space exploration (LDSE) missions will expose astronauts to multiple concurrent hazards that threaten physical and behavioral health, performance capacity, and mission success. However inspiring it may be, space exploration in any form is a physically dangerous and often life-threatening endeavor. NASA's Human Research Program identifies five principal hazards of human spaceflight

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(https://www.nasa.gov/hrp/hazards), including radiation, isolation and confinement, distance from Earth, gravity fields, and hostile and closed environments (Clément et al., 2020, Schorn and Roma, 2020). The interactions among spaceflight risks and countermeasures and their potential impacts on crew health and performance over time are only beginning to be understood by the research and operations communities.

NASA's Medical Operations community is responsible for maintaining crew health and performance readiness. In preparation for long-duration missions, NASA's Exploration Medical Capability Element anchors its research and countermeasure development efforts in the space medicine Exploration Medical Conditions List (EMCL), a list of 100 spaceflight medical conditions that have occurred in spaceflight, or are of significant concern for affecting crew survival or threatening mission objectives (Antonsen et al., 2017, Keenan et al., 2015, Watkins, 2010). However, in addition to spaceflight health and medical risks, NASA also considers the behavioral health and performance (BHP) risks of *Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders* and *Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation Within a Team* among the highest consequence risks of LDSE missions (National Aeronautics and Space Administration). The interactions between spaceflight medical conditions, their treatments, and crew behavioral health and performance functioning is not well understood, but is worthy of consideration by all stakeholders and supporters of human space exploration. In their call to change medical school education, the Institute of Medicine (2004) identified the importance of the link between behavioral and lifestyle factors influencing physical health, noting that 50% of morbidity and mortality in the United States is caused by behavior and lifestyle factors (Institute of Medicine (US) 2004). This reinforces the importance for the spaceflight medical community to consider these cross-links as well, which, in the context of spaceflight operations, includes recognition of the risks of comorbid behavioral health conditions (Read et al., 2017, Sinnige et al., 2013) and how spaceflight medical conditions and their treatments may contribute to behavioral health and performance risks (Figure 1).

Although some behavioral health conditions are tracked in the EMCL (e.g., Behavioral Emergency, Depression, Insomnia), there is a need to systematically evaluate potential BHP-relevant effects of *all spaceflight medical conditions* and *any potential side-effects* (e.g., behavioral health-related, known iatrogenic effects of treatment regimens) of each condition's primary course of treatment. Medically, BHP-relevant symptoms that may present across multiple conditions are rarely of value for differential diagnosis and treatment strategy (beyond actual behavioral health or psychiatric conditions), and BHP-relevant side-effects of medical treatments and medications are typically of secondary concern compared to resolving the primary medical condition. However, all meaningful sources of mission risk must be considered, regardless of disciplinary lines. Although it is widely acknowledged that BHP factors are cross-cutting and connected to most, if not all, spaceflight risks in the closed environments of spaceflight missions, a systematic, integrated assessment of the relationship between spaceflight medical conditions and BHP-relevant risks has not yet been conducted. Accurately characterizing the potential effects of medical conditions and their treatments on BHP-relevant outcomes can inform the evidence base to guide integrated research and countermeasure development while better informing NASA's integrated risk management strategies for spaceflight.

To this end, the primary goals of the present study were to systematically document (1) the BHP-relevant symptoms for each of the 100 EMCL medical conditions, (2) the BHP-relevant effects of the 105 spaceflight medical treatments in the current International Space Station (ISS) On-Orbit Medication List, and (3) the likelihood of potential BHP impacts from spaceflight medical treatments. To our knowledge, this is the first systematic assessment of spaceflight medical conditions' and treatments' potential impacts on behavioral health and performance risk.

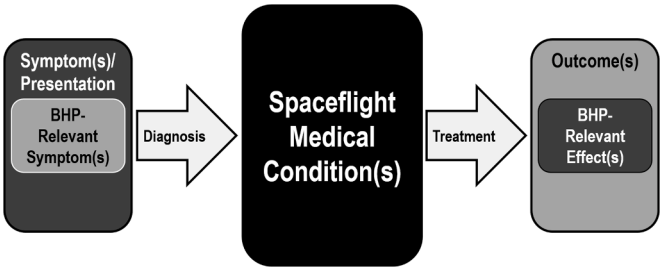

Figure 1. Potential sources of behavioral health and performance risks (inset figures) as symptoms of spaceflight medical conditions (left) and side-effects of their treatments (right).

2. METHOD

The primary methodology was literature and database search, review, and analysis of terrestrial medical reference data. We used NASA medical reference documents for spaceflight medical conditions, their prevalence, and treatments, with multiple standard medical databases based on terrestrial data for estimates of BHP-relevant symptoms of those medical conditions and BHP-relevant side-effects of medications used to treat them.

2.1. Defining BHP Symptoms and Effects

A critically important component of identifying BHP risks of spaceflight medical conditions and their treatments is defining what symptoms and side-effects are BHP-relevant. The medical reference literature uses varying, inconsistent, and often vague terminology for BHP-relevant symptoms and treatment effects. Moreover, similar symptoms appear in multiple database searches. To anchor our investigation, provide common terminology, and avoid over-estimation of BHP risks from repetition, we used the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) framework essentially as a content analysis filter to categorize each of the various symptoms and effects documented in the medical reference literature (Cuthbert and Kozak, 2013).

Although the primary goal of the RDoC framework is to elucidate the nature of mental health and illness, it does so not through a traditional symptom/category-based clinical diagnostic approach, but rather by defining the degree of (dys)function of core overlapping neurobehavioral systems ("domains") applicable to all individuals, teams, and situations (Clark et al., 2017, Landon et al., 2019). Broadly speaking, these domains encompass the neurobehavioral systems and functions subserving all behavioral health and performance risks. The six RDoC domains include the physical functions of the *Arousal and Regulatory Systems* and *Sensorimotor Systems* domains, as well as the psychological and social domains of *Negative Valence Systems, Positive Valence Systems, Cognitive Systems*, and *Social Processes*. As seen in Table 1, each domain contains several constructs and subconstructs.

For the present study, we limited our scope to the six primary domains. Specifically, each symptom and treatment effect identified and documented from the medical reference database search was categorized into one of the six RDoC domains based on the nature of the symptom or effect. For example, *Arousal and Regulatory* included symptoms reported as sleep/wake disturbances, fatigue, and hyperactivity; *Sensorimotor* included dizziness, ataxia, and impaired coordination; *Negative Valence* included anxiety, malaise, loss of appetite, and irritability; *Positive Valence* included mania; *Cognitive* included attention deficits, confusion, memory impairments, perceptual distortions, and psychosis; and *Social* included social withdrawal, aggression, and language/communication deficits.

Table 1
National Institute of Mental Health Research Domain Criteria (RDoC) framework (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml).

RDoC Domain	Construct	Subconstruct
Arousal/ Regulatory Systems	Arousal	
	Circadian Rhythms	
	Sleep and Wakefulness	
Sensorimotor Systems	Motor Actions	Action Planning and Selection
		Sensorimotor Dynamics
		Initiation
		Execution
		Inhibition and Termination
	Agency and Ownership	
	Habit	
	Innate Motor Patterns	
Negative Valence Systems	Acute Threat ("Fear")	
	Potential Threat ("Anxiety")	
	Sustained Threat	
	Loss	
	Frustrative Nonreward	
Positive Valence Systems	Reward Responsiveness	Reward Anticipation
		Initial Response to Reward
		Reward Satiation
	Reward Learning	Probabilistic and Reinforcement Learning
		Reward Prediction Error
		Habit
	Reward Valuation	Reward (Ambiguity/Risk)
		Delay
		Effort
Cognitive Systems	Attention	
	Perception	Visual Perception
		Auditory Perception
		Olfactory/Somatosensory/ Multimodal Perception
	Declarative Memory	
	Language	
	Cognitive Control	Goal Selection, Updating, Representation, and Maintenance
		Response Selection and Inhibition/Supression
		Performance Monitoring
	Working Memory	Active Maintenance
		Flexible Updating
		Limited Capacity
		Interference Control
Systems for Social Processes	Affiliation and Attachment	
	Social Communication	Reception of Facial Communication
		Production of Facial Communication
		Reception of Non-Facial Communication
		Production of Non-Factial Communication
	Perception and Understanding of Self	Agency
		Self-Knowledge
	Perception and Understanding of Others	Animacy Perception
		Action Perception
		Understanding Mental States

2.2. BHP Symptoms of Spaceflight Medical Conditions

The full list of 100 exploration medical conditions was taken from Keenan et al. (2015; also see Blue et al., 2019) (Keenan et al., 2015, Blue et al., 2019). To identify the presence and frequency of BHP symptoms of the EMCL conditions, we conducted a review of standard medical reference literature. The medical reference databases used for lists of symptoms were Medline Plus from the US National Library of Medicine (https://medlineplus.gov/), STAT!Ref (http://www.tetondata.com/product-srOnline.cshtml), and Access Medicine (https://accessmedicine.mhmedical.com/).

The terminology used for the various EMCL conditions is a mixture of names of symptoms, specific diagnoses, and groups of diagnoses. Since the exact names of each EMCL condition do not always yield results as database search terms, we developed a glossary with additional search terms based on related symptoms and diagnoses (e.g., "Chest Pain" and "Heart Attack" in addition to "Angina/Myocardial Infarction), simplified terminology (e.g., "Pancreatitis" in addition to "Acute Pancreatitis"), and alternate terminology (e.g., "The Bends" in addition to "Decompression Sickness Secondary to EVA"). A total of 20 conditions involving orthopedic injury, tissue damage, or trauma that did not yield search results fell under the search term "General Trauma/Injury", with BHP effects of pain as the primary symptom (described in Results below). A portion of EMCL conditions and associated search terms is presented below in Table 2 (for full list, see Supplementary Table 1).

Compilation of BHP-relevant symptoms of medical conditions was conducted by a project team member with expertise in behavioral health and psychiatry (Ph.D. in Neuroscience with Post-Doctoral Fellowship in Biological Psychiatry). Each of the 283 conditions/search terms was entered into each of the three medical reference databases for a total of 849 queries. The databases function as a search engine, with each keyword/phrase search producing a list of linked documents and articles sorted by relevance. Each reference document then summarizes the condition, including a list of symptoms. For each search term, we reviewed the first three reference documents listed in each of the three medical reference databases for a minimum of nine reference documents per medical condition. Most symptoms were included in the first document, but given the unstandardized and inconsistent terminology used in the medical reference literature to describe BHP symptoms, we included up to four reference documents per condition. BHP-relevant symptoms were extracted from a minimum of 2,547 medical reference documents. BHP relevance was determined if symptom descriptors included language used in RDoC Domains and Constructs (e.g., memory, sleep, social) or invoking behaviors, states, and processes associable to RDoC Domains and Constructs (e.g., withdrawal from activities, agitation, confusion, anorexia). Sensory/perceptual, motor/vestibular, or peripheral neurological symptoms such as numbness, tingling, dizziness, nausea, ataxia, and chills were not included unless they included a psychiatric component such as hallucinations or psychogenic symptoms. The symptom names and prevalence rates (when available) were recorded as presented in the medical reference literature.

2.3. BHP Effects of Spaceflight Medical Treatments

As with the search for BHP symptoms, the primary methodology for assessing BHP effects of spaceflight medical treatments was literature and database search, review, and analysis of medical data.

Since a Mars or other LDSE mission medical kit has not yet been finalized, we used the *ISS On-Board Medication List* (updated 2019-06-10) as our source of spaceflight medical treatments (courtesy NASA JSC Pharmacy, T.M. Bayuse, personal communication), and the *NASA Flight Surgeon Quick Reference Guide v1.7* to link spaceflight medical conditions with their treatments (courtesy NASA Medical Operations, N. G. Chough, personal communication).

To identify the presence and frequency of BHP effects of spaceflight medical treatments, we conducted a review of the medical reference literature. The medical reference database used for the list of medications was Lexicomp (https://www.wolterskluwercdi.com/solutions/; https://online.lexi.com).

The full ISS On-Board Medication List includes a total of 112 treatments. The following medications containing Acetaminophen, Epinephrine, Lidocaine, and Sodium Chloride were all included in the

Table 2
List of Exploration Medical Conditions List spaceflight medical conditions and associated search terms used to identify behavioral health and performance-relevant symptoms.

Exploration Medical Conditions and Treatments		
EMCL Conditions	**Example Additional Search Terms**	**ISS On-Board Medication (s)**
Angina/Myocardial Infarction, Hypertension, Sudden Cardiac Arrest	Chest Pain, High Blood Pressure, Cardiac Arrest	Lisinopril (Zestril)
Abscess, Avulsion (Tooth Loss), Caries	Tooth Abscess, Toot Avulsion, Tooth Decay	Hydrocodone and Acetaminophen (Vicodin HP)
Skin Abrasion, Skin Infection, Skin Rash	General Trauma/Injury, Dermatitis, Irritant Dermatitis	Loratadine (Claritin), Clindamycin (Cleocin)
Indigestion, Appendicitis, Hemorrhoids	Gallstones, Diverticulitis, Pancreatitis	Omeprazole (Prilosec), Ondansetron (Zofran ODT), Bisacodyl (Dulcolax)
Influenza, Allergic Reaction, Herpes Zoster	Allergy, Shingles, Flu	Metronidazole (Flagyl), Azithromycin (Zithromax)
Anxiety, Insomnia, Depression	Psychiatric Emergency, Anxiety Disorders, Insomnia and Excessive Daytime Sleepiness (EDS)	Melatonin, Naloxone (Narcan), Modafinil (Provigil)
Head injury, Space Motion Sickness, Seizures	Numbness and tingling, Frontal Lobe Seizures, Motion Sickness	Promethazine (Phenergan), Ketamine (Ketalar)
Eye Infection, VIIP, Eye Abrasion	Acute Angle-Closure Glaucoma, General Trauma/Injury, Conjunctivitis	Acetazolamide (Diamox), Olopatadine (Pataday)
Ankle Sprain/Strain, Shoulder Dislocation, Knee Sprain/Strain	General Trauma/Injury, Distal Radius Fracture, Broken Wrist	Diazepam (Valium), Ciprofloxacin and Dexamethasone (CiproDex)
Abdominal injury, Acute Compartment Syndrome, Back Injury	General Trauma/Injury, Inguinal Hernia, Incisional Hernia	Ondansetron (Zofran ODT)
Acute Sinusitis, Hearing Loss, Nasal Congestion	Ear Barotrauma, Stuffy or runny nose, Epistaxis	Pseudoephedrine (Sudafed), Sodium Chloride Flush (Normal Saline), Oxymetazoline (Afrin)
Acute Arthritis, Back Pain, Headache	Tension-Type Headaches, Osteoarthritis, Low Back Pain	Ibuprofen (Motrin), Acetaminophen (Tylenol), Diphenhydramine (Benadryl)
Altitude Sickness, Respiratory Infection, Decompression Sickness Secondary to EVA	Acute Mountain Sickness, The Bends, Sore Throat	Lidocaine (Xylocaine), Aspirin, Amoxicillin (Amoxil)
Acute Radiation Syndrome, Toxic Exposure: Ammonia, Smoke Inhalation	Radiation Sickness, Adverse Drug Reaction, Pulmonary edema	Fluconazole (Diflucan)
Urinary Tract Infection, Vaginal Yeast Infection, Urinary Incontinence	Bladder Control Problems, Kidney Stones, Candidiasis	Ceftriaxone (Rocephin)

search as separate medications since they differ in formulation(s) or route(s) of administration: Acetaminophen (Acetaminophen [Tylenol], Hydrocodone & Acetaminophen [Vicodin HP]), Epinephrine (Epinephrine, Epinephrine [EpiPen]), Lidocaine (Lidocaine [Xylocaine], Lidocaine Jelly [Xylocaine], Lidocaine with Epinephrine [Xylocaine with Epinephrine]), and Sodium Chloride (Sodium Chloride, Sodium Chloride [Ayr Saline]), Sodium Chloride Flush [Normal Saline]).

However, seven medications are part of more than one on-board medication "pack," so they were only searched once and the redundant entries were removed. These included Acetazolamide ER (Diamox), Aspirin, Diphenhydramine (Benadryl) Fexofenadine (Allegra), Modafinil (Provigil), Prednisone (Deltasone), and Promethazine (Phenergan).

Thus, the total number of spaceflight medical treatments included in the search was 105. Each medication's generic and brand name (as applicable) were entered into the Lexicomp database. The BHP-relevant effects and prevalence rates (when available) as presented in the medical reference literature were recorded. A total of 733 BHP-relevant effects across all treatments were documented. Prevalence data of BHP-relevant effects of spaceflight medical treatments were available for 290 (39.6%) of the 733 documented BHP effects. The remainder lacked prevalence data and thus were counted as "always present", despite the possibility of these effects not occurring in 100% of patients. Furthermore, we do not have severity measures for the BHP effects and thus mild and major effects are weighed equally. Considering this, our measure may inflate the possibility of actual risk of an adverse event.

2.3.1. BHP Potential Impact Breadth from Treatments

Given the limited and inconsistent prevalence data in the medical reference literature on BHP effects, we developed a crude metric to estimate the breadth of potential BHP impacts from treating spaceflight medical conditions. Specifically, for each of the 105 medical treatments, we multiplied the number of EMCL conditions (1-100) for which the treatment is used (according the *NASA Flight Surgeon Quick Reference Guide*) by the number of RDoC neurobehavioral domains (0-6) with documented potential BHP effects. The minimum raw value of 0 means the treatment has no established BHP effects regardless of how many medical conditions for which it is used. A maximum raw value of 600 means a treatment is used for all 100 conditions, and that particular treatment may increase risk across all 6 BHP domains. For ease of interpretation, all results were normalized to a 0-100 scale per the formula below:

BHP Impact Breadth from Treatments = [(EMCL conditions used x RDoC domains with documented BHP effects) / 600] x 100

2.3.2. BHP Potential Impact Likelihood from Treatments

In order to estimate the likelihood of a medical treatment-induced BHP impact in spaceflight operations, we developed an evidence-based BHP Potential Impact Likelihood metric representing the number of times per person-year a BHP-relevant effect of medical treatments may be produced.

This measure was anchored in the results of NASA's Lifetime Surveillance of Astronaut Health (LSAH) data request #10912 presented in full in Appendix Table 1 of Antonsen et al. (2017) evidence review of spaceflight medical conditions risk (Antonsen et al., 2017). This included all 381 documented medical conditions, symptoms, and complaints from all International Space Station (ISS) missions through Expedition 40. We took each medical incident and matched it to a corresponding EMCL condition. We then took each spaceflight medical treatment and mapped the per person-year incidence rates of all medical conditions for which the treatment may be used. Each spaceflight medical treatment then yielded a cumulative per person-year incidence rate of potential use. For each treatment, that cumulative incidence rate was then multiplied by the number of RDoC neurobehavioral domains with documented side effects per the formula below:

BHP Impact Likelihood from Treatments = (Cumulative incidence rate of EMCL conditions used) x (RDoC domains with documented BHP effects)

The resulting BHP Potential Impact Likelihood metric broadly estimates the number of times per person-year that each medication could be used and potentially produce an adverse BHP effect. This estimation metric is necessary due a lack of comprehensive prevalence estimates for inflight medication use.

3. RESULTS

3.1. BHP Symptoms of Spaceflight Medical Conditions

3.1.1. BHP Effects of Pain

A total of 20 exploration medical conditions involving orthopedic injury, tissue damage, and trauma that did not yield search results fell under the search term "General Trauma/Injury," with pain as the primary symptom. An additional 40 conditions included documented BHP symptoms as well as pain or symptoms defined by pain (e.g., headache) (McCracken and Iverson, 2001).

Naturally, pain is a defining diagnostic symptom of many medical conditions, including those in spaceflight, and physical impairment can constitute a meaningful risk to safety, health, and mission performance given the physical hazards of the spaceflight environment and sustained physical demands of mission operations. However, pain itself can produce BHP-relevant symptoms, mostly in the *Cognitive Systems* domain, which can contribute to mission risk given the extensive cognitive demands of spaceflight mission operations.

Pain is an aversive subjective experience (sensation) indicating actual or potential tissue damage. As a survival mechanism (Broom, 2001), pain demands attention and consumes attentional and cognitive resources (Eccleston and Crombez, 1999, Moriarty et al., 2011, Pais--Vieira et al., 2009). It is hypothesized that cognition and pain processing can modulate one another as their supporting neural regions are tightly interconnected through a wide, distributed brain network. Pain processing is associated with six regions in particular: somatosensory cortical areas 1 and 2, thalamus, prefrontal cortex, insular cortex, and the anterior cingulate cortex (Apkarian et al., 2005). Patients with chronic musculoskeletal pain demonstrate altered structural and functional connectivity in many of these brain regions (Iwabuchi et al., 2020, Ng et al., 2017, Zhang et al., 2019), suggesting that neuroplastic alterations coincide with cognitive performance repercussions of pain.

Indeed, pain is associated with multiple cognitive decrements, primarily in attention, processing speed, and memory. Pain patients have shown impairments in attentional switching and attentional interference tasks (Grisart and Plaghki, 1999), which may be due to impaired top-down cognitive control making it more difficult to inhibit irrelevant stimuli (Legrain et al., 2009). Pain also impairs speed of information processing and psychomotor ability, with slower reaction times compared to healthy controls in psychomotor tasks (Harman and Ruyak, 2005, Sjøgren et al., 2005). Additionally, learning and memory problems are frequently reported by chronic pain patients, who exhibit impaired tactile learning (Maihöfner and DeCol, 2007) and poorer performance on working memory, verbal and non-verbal memory, and visuospatial tasks (Luerding et al., 2008, Oosterman et al., 2011).

Given the range of potential cognitive effects of pain, all 60 exploration medical conditions with pain as a symptom in the medical reference literature were documented with *Cognitive Processes* as a BHP-relevant symptom.

3.1.2. BHP Symptoms of Spaceflight Medical Conditions

Including the effects of pain, 32% of the 100 spaceflight medical conditions include symptoms relevant to *Arousal and Regulatory Systems* (e.g., sleep/wake disturbances, fatigue, hyperactivity), 22% include symptoms relevant to *Sensorimotor Systems* (e.g., dizziness, ataxia, impaired coordination), 42% include symptoms relevant to *Negative Valence Systems* (e.g., anxiety, malaise, irritability, loss of appetite), 6% include symptoms relevant to *Positive Valence Systems* (e.g., mania), 94% include symptoms relevant to *Cognitive Systems* (e.g., attention deficits, confusion, psychosis), and 11% include symptoms relevant to *Social Processes* (e.g., social withdrawal, aggression, language/communication deficits; Figure 2).

Separate from the BHP effects of pain, we recorded a total of 512 BHP-relevant symptoms across all conditions from all sources. Since the medical reference documents focus on symptoms and diagnostic criteria, prevalence of most symptoms was rarely included. Of the 512 documented BHP symptoms across the 100 medical conditions, prevalence data were only available for four symptoms in three conditions. This included condition *Angina/Myocardial Infarction* (symptom *Confusional State*, prevalence *Less Common*), condition *Anxiety* (symptom *Worry or Tension*, prevalence *Frequent*), and condition *Appendicitis* (symptom *Anorexia*, likelihood ratio LR+1.27, LR-0.59 and prevalence *70% Frequency*).

As seen in Figure 3, across neurobehavioral domains, 5% of spaceflight medical conditions include BHP symptoms from all six domains, 0% of conditions include symptoms from five domains, 9% include symptoms from four domains, 20% include symptoms from three domains, 17% include symptoms from two domains, 47% include symptoms from one domain; only 2% of conditions have no established BHP symptoms (conditions *Herpes Zoster* and *Nose Bleed [SAS]*).

3.2. BHP Effects of Spaceflight Medical Treatments

3.2.1. BHP Effects of Spaceflight Medical Treatments

A total of 733 effects across all treatments/medications were documented. Of the 105 spaceflight medical treatments, 62.9% (n=66) affect *Arousal and Regulatory Systems*, 60.0% (n=63) affect *Sensorimotor Systems*, 53.3% (n=56) affect *Negative Valence Systems*, 38.1% (n=40) affect *Positive Valence Systems*, 59.1% (n=62) affect *Cognitive Systems*, and

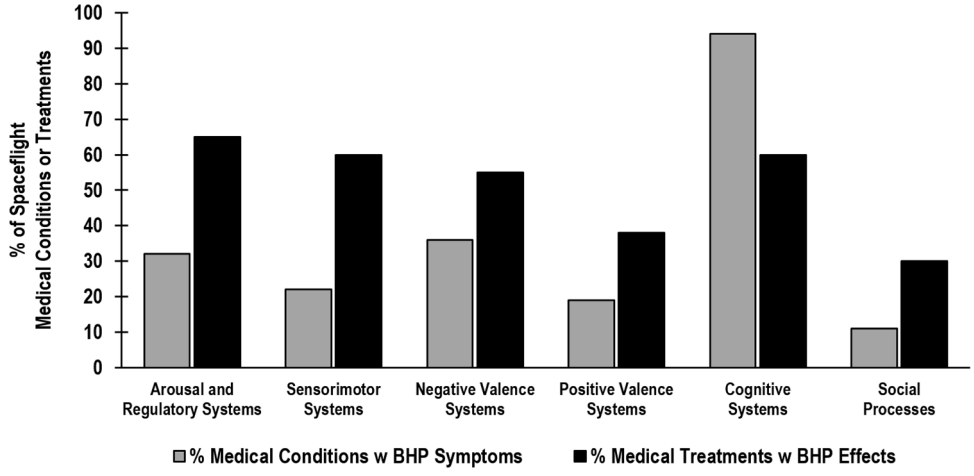

Figure 2. Percentage (y-axis) of 100 exploration medical conditions (gray) and 105 spaceflight medical treatments (black) with BHP impacts across RDoC neurobehavioral domains (x-axis).

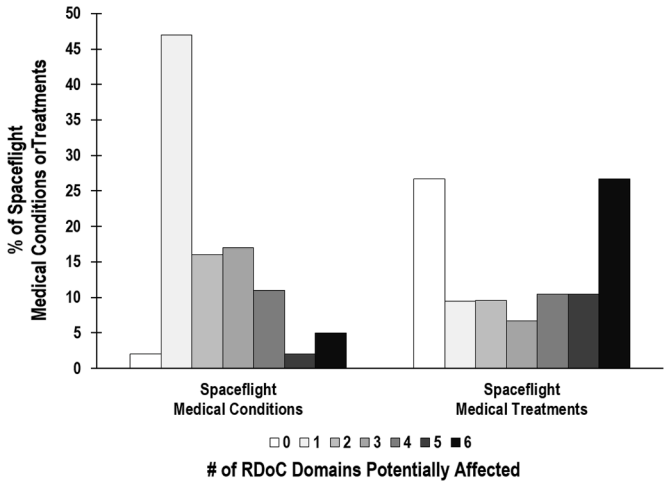

Figure 3. Percentage (y-axis) of spaceflight medical conditions (x-axis left) and treatments (x-axis right) with BHP-relevant symptoms or effects potentially impacting 0, 1, 2, 3, 4, 5, or 6 RDoC domains (Arousal and Regulatory Systems, Sensorimotor Systems, Negative Valence Systems, Positive Valence Systems, Cognitive Systems, and Social Processes). A majority (98%) of the 100 exploration medical conditions include at least one BHP-relevant symptom, with 5% including symptoms across all six domains. Of the 105 spaceflight medical treatments, 73% may produce at least one BHP-relevant effect, with 27% producing effects across all six domains.

31.4% (n=31) affect *Social Processes* (Figure 2).

Prevalence data were available for 290 (39.6%) of the 733 documented BHP effects. Documentation on prevalence rates varied for any given side-effect, including maximum thresholds (e.g., <8% fatigue for Valacyclovir [Valtrex]), minimum thresholds (e.g., >1% vertigo for Lisinopril [Zestril]), specific rates (e.g., 3% memory impairment for Zolpidem [Ambien]), narrow ranges (e.g., 19-21% headache for Tamsulosin [Flomax]), and wide ranges (e.g., 9-27% headache for Ondansetron [Zofran ODT]). Of the 290 reported prevalence rates of BHP-relevant side-effects, 24.1% (n=70) were ≤1%; the highest prevalence rate for any BHP-relevant effect was up to 38% headache (pain) for Valacyclovir (Valtrex).

Across neurobehavioral domains, 26.7% (n=28) of spaceflight medical treatments affect all six domains, 10.5% (n=11) of medications affect five domains, 10.5% (n=11) affect four domains, 6.7% (n=7) affect three domains, 9.5% (n=10) affect two domains, and 9.5% (n=10) affect one domain; the remaining 26.7% (n=28) of medications have no established BHP effects (Figure 3).

3.2.2. BHP Potential Impact Breadth from Treatments

Figure 4 presents the BHP potential impact breadth values for all treatments with positive values (26 treatments had values = 0). A total of 53.3% of treatments (n=56) had values ≤1, 27.6% (n=29) treatments had values between 1-5, 12.4% (n=13) between 6-10, and 6.7% (n=7) >10. The five treatments with the highest combination of medical condition application and BHP domains potentially impacted are (1) Ibuprofen (Motrin; 29.0), (2) Hydrocodone and Acetaminophen (Vicodin HP; 20.8), (3) Sulfamethoxazole and Trimethoprim (Bactrim DS; 17.0), (4) Promethazine (Phenergan; 16.7), and (5, tie) Dexamethasone (Decadron) and Hydromorphone (Dilaudid; 15.0).

3.2.3. BHP Potential Impact Likelihood from Treatments

Figure 5 below presents the BHP potential impact likelihood estimates for all treatments with positive values (36 treatments had values = 0). Across treatments, we broadly estimate a total of 481 times per person-year that a spaceflight medical condition and its subsequent treatment could produce an adverse BHP effect. The five treatments with the highest combination of cumulative medical condition prevalence rates and BHP domains potentially impacted are (1) Ibuprofin (Motrin; 81.8 incidents/person-year), (2) Hydrocodone and Acetaminophen (Vicodin HP; 49.9 incidents), (3) Dexamethasone (Decadron; 33.8), (4) Promethazine (Phenergan; 24.5), and (5) Diphenhydramine (Benadryl; 23.4)

4. DISCUSSION

Long-duration space exploration (LDSE) missions will expose astronauts to multiple interacting hazards that threaten physical and behavioral health, performance capacity, and mission success. These risks are both inherent to the LDSE enterprise, and may impact physical and behavioral health independently (e.g., radiation, microgravity, physical workload), but in the closed system of spaceflight, the countermeasure strategies used to mitigate one set of risks can also inadvertently create or increase another set of risks to crew health, safety, and performance.

The purpose of the present study was to examine the interactions between spaceflight medical operations and behavioral health and performance (BHP) risks. To our understanding, this was the first systematic attempt to characterize the potential BHP impacts of spaceflight medical conditions and their treatments, independently of the inherent BHP risks of LDSE. In effect, this was an assessment of the additive BHP risk conferred by spaceflight medical conditions and their treatments, and of the risk trades involved in potentially producing or exacerbating BHP risks by reducing medical risks.

Using standard medical reference databases and NASA Medical Operations reference materials, we documented the presence and estimated frequency of BHP-relevant symptoms for each of the Exploration Medical Conditions and the BHP-relevant effects of the medical treatments in the ISS On-Orbit Medication List. Including the effects of pain, 98% of all Exploration Medical Conditions include at least one BHP-relevant symptom, most commonly within the *Cognitive Systems* domain (e.g., attention deficits, confusion, psychosis). Just between *Cognitive Systems* symptoms and 22% of conditions with symptoms relevant to *Sensorimotor Systems* (e.g., dizziness, ataxia, impaired coordination), the connection for mission performance risk is clear.

Excluding insomnia, the five most frequent medical conditions astronauts experience in-mission are space adaptation-related nasal congestion, back pain, motion sickness, headache, and constipation (Antonsen et al., 2017, 6). Astronaut journals also reveal relative frequency of pain or discomfort from musculoskeletal and skin injuries or irritation (Stuster, 2016). All of these conditions have potential cognitive ramifications, and some can also impact *Arousal and Regulatory* (e.g., congestion and space adaptation motion sickness) and *Negative Valence Systems* (e.g., headache and space adaptation motion sickness). Such conditions can easily be minimized as relatively benign and treatable; however, similar ailments (e.g., chronic sinusitis or low back pain) are established contributors to BHP decrements among the general population (Campbell et al., 2017, Magni et al., 1994). Thus, it is clear that common spaceflight medical conditions can have secondary BHP impacts. As one anonymous ISS astronaut stated: “It’s amazing how health affects the mood here” (Stuster, 2016).

Reducing physical and performance risks by treating and resolving underlying medical conditions is critical, and our assessment of BHP side-effects of spaceflight medical treatments also reveals considerable BHP risks from the treatments themselves. With the exception of *Cognitive Systems*, the proportion of medical treatments with detrimental BHP effects was greater than the proportion of medical conditions with BHP-relevant symptoms. The distribution of BHP effects across treatments was also bimodal, in that 27% of treatments have no established BHP impacts, yet another 27% have the potential for wide-ranging effects across all six neurobehavioral domains. For example, acetaminophen has no established BHP impacts; however, ibuprofen has the potential to impact all six BHP domains, although the severity of those potential impacts is not clear. Sleep medications are likewise of

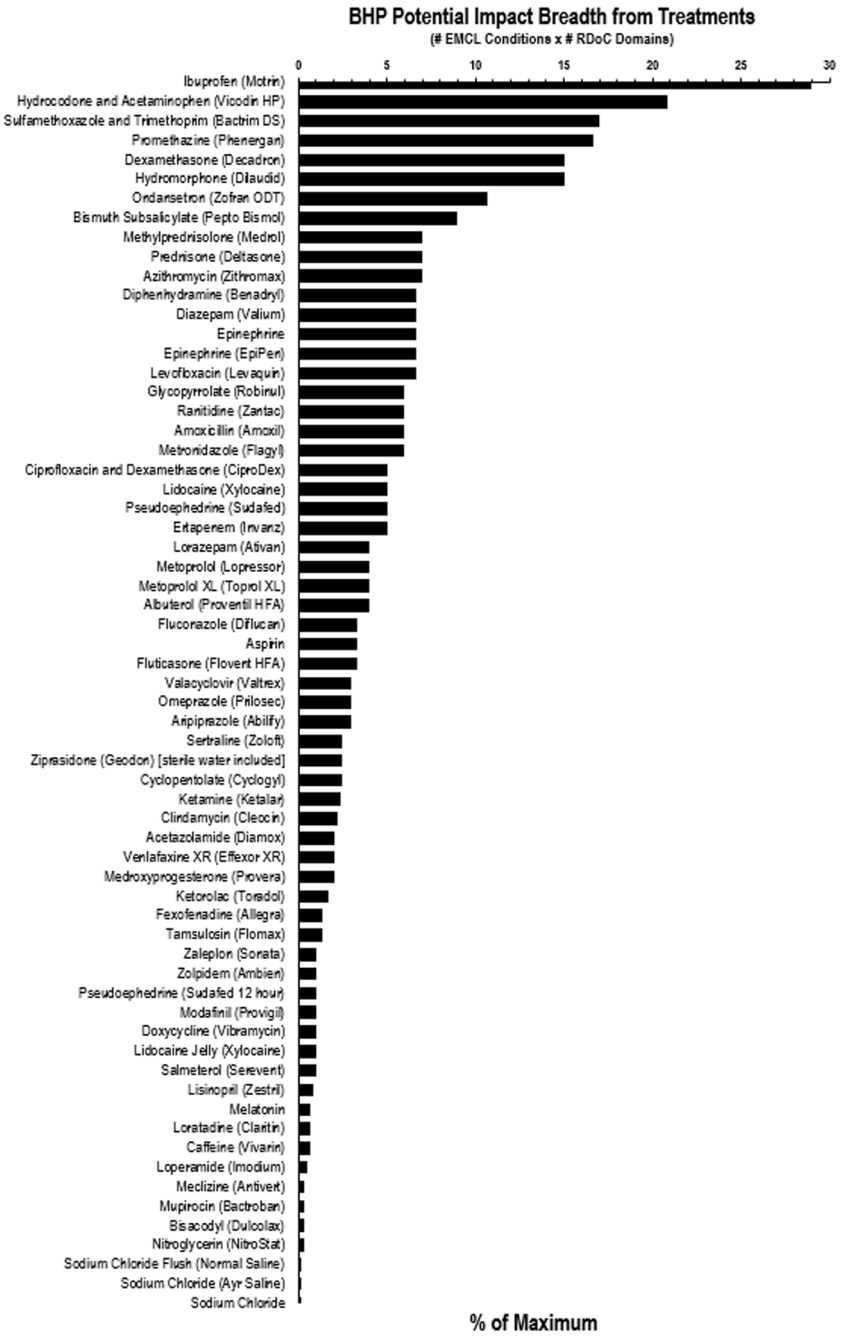

Figure 4. BHP potential impact breadth of spaceflight medical treatments. For each medication (y-axis), the value (x-axis) represents the % of maximum breadth of documented impacts across RDoC neurobehavioral domains. A value of 0 indicates no documented BHP effects regardless of how many conditions for which the treatment is used. A value of 100 indicates the treatment is used for all spaceflight medical conditions and has documented potential impacts on all BHP domains.

particular BHP relevance; they are simultaneously a preventative countermeasure or treatment for sleep-related cognitive decrements, but may produce secondary effects across all six BHP symptom domains. There is also some evidence to suggest that sleep aid medications may not result in optimal, restorative sleep (Barger et al., 2014), potentially altering risk-benefit decisions, at least regarding the behavioral medicine and sleep risks of spaceflight. Alternatively, untreated insomnia may also impair cognition, mood, and team performance. It is for this reason that despite the potential for BHP adverse effects, the risk-benefit for many spaceflight conditions may fall in favor of the countermeasure use. Taken together, this suggests of first, being alert to, and secondly, using that information to weigh the risk-benefits of medical treatments during spaceflight, at least as it relates to both medical and BHP risk management for LDSE missions.

The value of documenting the potential breadth of BHP impacts from medical conditions and their treatments must be balanced by an understanding of likelihood. Reliable estimates of inflight medication use and adverse effects across treatments are limited (Wotring and Smith, 2020, Wotring, 2015), although medication use in general is estimated to be quite high, with 78-94% of Space Shuttle astronauts taking at least one medication on orbit (Putcha et al., 1999, Santy and Bungo, 1991). The most frequently used medications have been for the treatment of space adaptation motion sickness, sleep challenges, headache, and back pain (Wotring, 2015, Putcha et al., 1999, Santy and Bungo, 1991). Sleep medications are a commonly utilized countermeasure for circadian disruption and space adaptation insomnia, being taken on 52% of

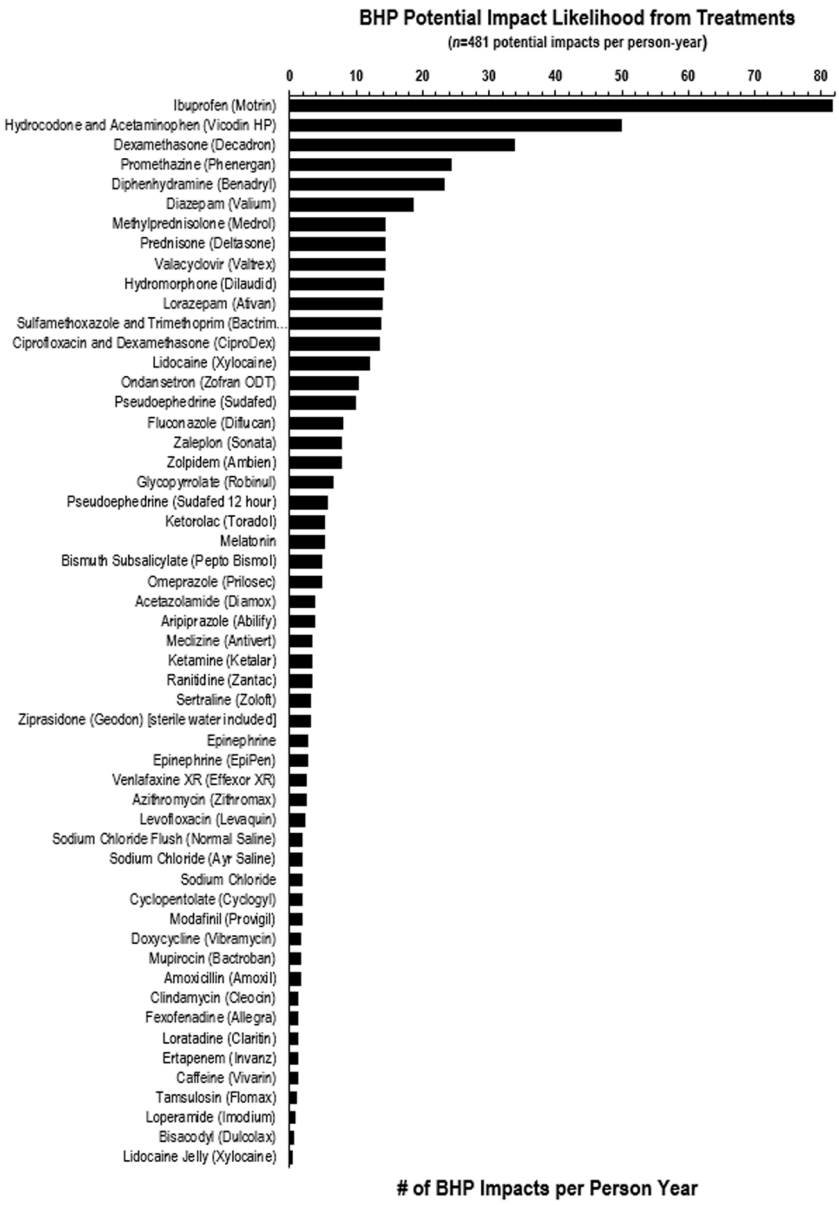

Figure 5. BHP potential impact likelihood of spaceflight medical treatments. For each treatment (x-axis), the value (y-axis) represents the # of BHP Impacts from Treatments per Person-Year in spaceflight.

in-mission nights by any crewmember (Barger et al., 2014). In lieu of consistent records of medication use, the BHP potential impact likelihood metric is rooted in the prevalence of reported spaceflight medical incidents over 14 years of ISS operations, with potential BHP impacts based on the recommended treatments for those conditions. If the prevalence of spaceflight medical conditions in ISS is equally likely for LDSE missions, and treatments are administered every time, then we estimate the potential for 481 adverse BHP-relevant effects per person-year. Even if treatments are used only half the time, or not all applicable treatments are used for each incident, there remains the potential for thousands of adverse BHP impacts across a single multi-person, multi-year LDSE mission. With surface operations and extra-vehicular activity (EVA) for lunar and Mars missions projected at over 20 hours per week (Abercromby et al., 2019), LDSE missions will likely see a significantly increased prevalence of orthopedic conditions marked by pain (and the cognitive impact thereof) as well as the adverse BHP effects of any subsequent treatments.

As intriguing as this analysis is, it is only a first attempt and very high-level overview of medical and BHP risk interactions. Our estimations of medical and BHP risk interactions, however systematic, are at best a starting point. Among the limitations is our reliance on terrestrial clinical medical data for BHP impacts. The descriptions of deficits in the medical reference literature were almost always imprecise; although suitable for assignment to one of the six neurobehavioral domains, the exact nature of some deficits is unclear, despite clear operational relevance (e.g., are "cognitive difficulties" deficits in working memory, procedural memory, attention, cognitive flexibility, etc.?). A better understanding of the exact nature and likelihood of adverse BHP effects of spaceflight medications is warranted, further compounded by the knowledge gap on stability, potency, pharmacokinetics, and adverse effects specifically in the spaceflight environment (Wotring and Smith, 2020, Kast et al., 2017). Even with more clearly defined effects, it is also important to note that none of the BHP symptoms or treatment impacts were weighted by likelihood or severity of those effects. For example, specific symptoms and side-effects such as insomnia, headache, psychosis, irritability, and suicidal ideation were all documented in the medical reference literature as possible, but without reliable prevalence data, all counted as equally likely and

impactful. However rare psychosis or suicidal ideation adverse events are, even a single episode constitutes a much greater risk to crew health and safety than repeated increases in negative mood. A more precise and integrated, evidence-based understanding of medical and BHP risk interactions will be essential for informing trade-spaces involved in the design of an LDSE formulary, medical kits, and medical decision-making support systems.

Despite the limitations, it is our hope that systematic examination of behavioral health and performance impacts of spaceflight medical conditions and their treatments can inform integrated mission planning, countermeasure development, design specifications, resource/payload allocation, and operational decision-making for LDSE missions. Ultimately, a more complete understanding of how the LDSE mission environment affects the body and brain—including what we do to mitigate those effects—can then guide the development of effective mission architectures, habitats, and medical support systems for those who work, live, serve, and explore on the final frontier.

Declaration of Competing Interest

The authors of this report are entirely responsible for its content. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the US Government, the National Aeronautics and Space Administration, KBR, Stony Brook University, the University of California, Los Angeles, the Department of Defense, or Leidos. The authors have no interests that may be perceived as conflicting with the work described or proposed here. The authors declare no competing interests. Author contributions: TJW conceived the project. PGR, JSS, and TJW designed the study. JSS, JMS, LBL, SEW, and PGR collected the data. PGR, SEW, LBL, and JMS analyzed the data. PGR, JMS, SEW, and TJW drafted the manuscript. All authors made substantial contributions and approved the final version of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lssr.2021.05.006.

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