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The Impact of Sex and Gender on Adaptation to Space: Executive Summary

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Abstract

This review article is a compendium of six individual manuscripts, a Commentary, and an Executive Summary. This body of work is entitled ''The Impact of Sex and Gender on Adaptation to Space'' and was developed in response to a recommendation from the 2011 National Academy of Sciences Decadal Survey, ''Recapturing a Future for Space Exploration: Life and Physical Sciences for a New Era,'' which emphasized the need to fully understand sex and gender differences in space. To ensure the health and safety of male and female astronauts during long-duration space missions, it is imperative to examine and understand the influences that sex and gender have on physiological and psychological changes that occur during spaceflight. In this collection of manuscripts, six workgroups investigated and summarized the current body of published and unpublished human and animal research performed to date related to sex- and gender-based differences in the areas of cardiovascular, immunological, sensorimotor, musculoskeletal, reproductive, and behavioral adaptations to human spaceflight. Each workgroup consisted of scientists and clinicians from academia, the National Aeronautics and Space Administration (NASA), and other federal agencies and was co-chaired by one representative from NASA and one from the external scientific community. The workgroups met via telephone and e-mail over 6 months to review literature and data from space- and ground-based studies to identify sex and gender factors affecting crew health. In particular, the Life Sciences Data Archive and the Lifetime Surveillance of Astronaut Health were extensively mined. The groups identified certain sex-related differences that impact the risks and the optimal medical care required by space-faring women and men. It represents innovative research in sex and gender-based biology that impacts those individuals that are at the forefront of space exploration.

Introduction and Process

Sex and gender significantly influence health on Earth and in space. To ensure the health and safety of male and female astronauts during long-duration space missions, it is imperative to examine and understand the influences that sex and gender have on physiological and psychological changes that occur during spaceflight.

For over 20 years, there has been an increased effort to comprehend how men and women are similar and different in all aspects of health. Federal agencies have policies to ensure that men and women are included in clinical trials and that findings are evaluated for sex- and gender-based differences. In the 2001 Institute of Medicine report ''Does Sex Matter,''[1] ''sex'' was defined as the classification of male or female according to an individual's genetics and ''gender'' refers to

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a person's self-representation as male or female based upon social interactions.

The National Aeronautics and Space Administration (NASA) sponsored a workshop with the University of Missouri in 2002 and published its findings in ''Sex, Space and Environmental Adaptation: A National Workshop to Define Research Priorities Regarding Sex-Differences in Human Responses to Challenging Environments.''[2] The findings included a comprehensive review of existing data and recommendations to fill gaps in NASA's knowledge base.

The 2011 National Academy of Sciences Decadal Survey ''Recapturing a Future for Space Exploration: Life and Physical Sciences for a New Era''[3] emphasized the need to fully understand sex and gender differences. In response, in 2013, NASA and the National Space Biomedical Research Institute (NSBRI) commissioned a study that resulted in a workshop and this report.

In this study, six workgroups investigated the current body of published and unpublished human and animal research performed to date related to sex- and gender-based differences in the areas of cardiovascular, immunological, sensorimotor, musculoskeletal, reproductive, and behavioral adaptations to human spaceflight. Each workgroup consisted of scientists and clinicians from academia, NASA, and other federal agencies and was co-chaired by one representative from NASA and one from the external scientific community. The workgroups met by telephone and e-mail over 6 months to review literature and data from space- and ground-based studies to identify sex and gender factors affecting crew health. In particular, the Life Sciences Data Archive (LSDA) and the Lifetime Surveillance of Astronaut Health (LSAH) were extensively mined.[4,5] NASA and NSBRI co-hosted a public virtual workshop on June 25, 2013,[6] in which the workgroup co-chairs presented key findings and recommendations for biomedical research priorities.

The remainder of this executive summary provides a synopsis of the key findings and recommendations provided by the six workgroups.

Results and Key Findings

Key demographics

As of June 2013, the demographics of the international astronaut and cosmonaut population indicated that a total of 534 humans have flown in space—477 men and 57 women (approximately 11% of the total).[7,8] A total of 129 NASA astronauts have flown to the International Space Station (space station), comprising 103 men and 26 women (approximately 20% of the total). Female NASA space station astronauts are on average 2 years younger than male astronauts. While there were no significant differences in the percentage of male (76%) and female space station astronauts (69%) who were married, a significantly greater percentage of male astronauts had a least one child (67% versus 38%) and overall, men had more children than women. From a professional perspective, female NASA space station astronauts have almost twice as many doctorate-level degrees as their male counterparts (50% versus 28%); conversely male NASA space station astronauts had more military experience (73% versus 39%). Sex and gender differences as well as these social determinants could impact adaptation to spaceflight.

Cardiovascular

On Earth, cardiovascular (CV) disease is the leading cause of death in women and men, with women developing coronary heart disease about a decade later than their male peers.[9] Although sex and gender gaps continue to narrow, women continue to have greater cardiovascular morbidity and mortality, in part because they do not consistently receive optimal preventive strategies, diagnostic procedures, and treatments.[10–12] Differences in CV disease on Earth warrant examination of these issues in space.

While there has been a paucity of sex- and gender-based research in this area in space, there have been several notable findings during the past decade (Fig. 1). One important finding is that women experience immediate post-flight orthostatic intolerance, which is the inability to stand without fainting for protracted periods. This condition is more prevalent in female astronauts compared to their male counterparts.[13–16] A possible mechanism for this sex-based difference is that women have reduced leg vascular resistance as shown during bed rest, which is used as an analog for microgravity.[16] Additionally, women have greater loss of plasma volume than men during spaceflight.[16] There are other known sex differences affecting the cardiovascular system. For example, in response to stress, women characteristically respond with an increase in heart rate and men respond with an increase in vascular resistance.[17] Space implications of these Earth observations require further study.

The visual impairment intracranial pressure (VIIP) syndrome is currently one of the most serious spaceflight-related health risks.[18] VIIP manifests with anatomical ocular changes, ranging from mild (e.g., globe flattening) to clinically significant (e.g., optic disc edema) symptoms, with a range of corresponding changes in visual function (e.g., hyperopic shifts to enlarged blind spots). In two affected crew members, post-flight lumbar punctures indicated elevated intracranial pressure (ICP) (i.e., >25 cm H_2O). Prolonged elevation of ICP can cause long-term loss of visual acuity and potentially also impact neurological function.[19]

NASA has a newly developed research program aimed at identifying the underlying pathophysiology of VIIP, which would then allow for countermeasure development. Currently, 82% of male astronauts are affected (14 out of 17 studied) versus 62% of female astronauts (5 out of 8 studied). This difference is not statistically significant, potentially due to the small number of subjects (particularly female astronauts) studied to date. All clinically significant cases described thus far have occurred in male astronauts,[20,21] while female astronauts have exhibited much milder visual impairment symptoms. The observation that clinically significant cases of visual impairment have occurred only in male astronauts may be related to several factors including higher vascular compliance in women, which could be protective, and the slightly younger age of female astronauts compared with male astronauts. Sex hormone–related differences could impact vascular compliance and plasma volume alterations. Research is underway to better understand individual susceptibilities (including sex differences) as well as environmental and behavioral factors associated with the VIIP syndrome.

Immunologic

Earth-based studies suggest sex differences in immune responses. Women mount a more potent immune response than

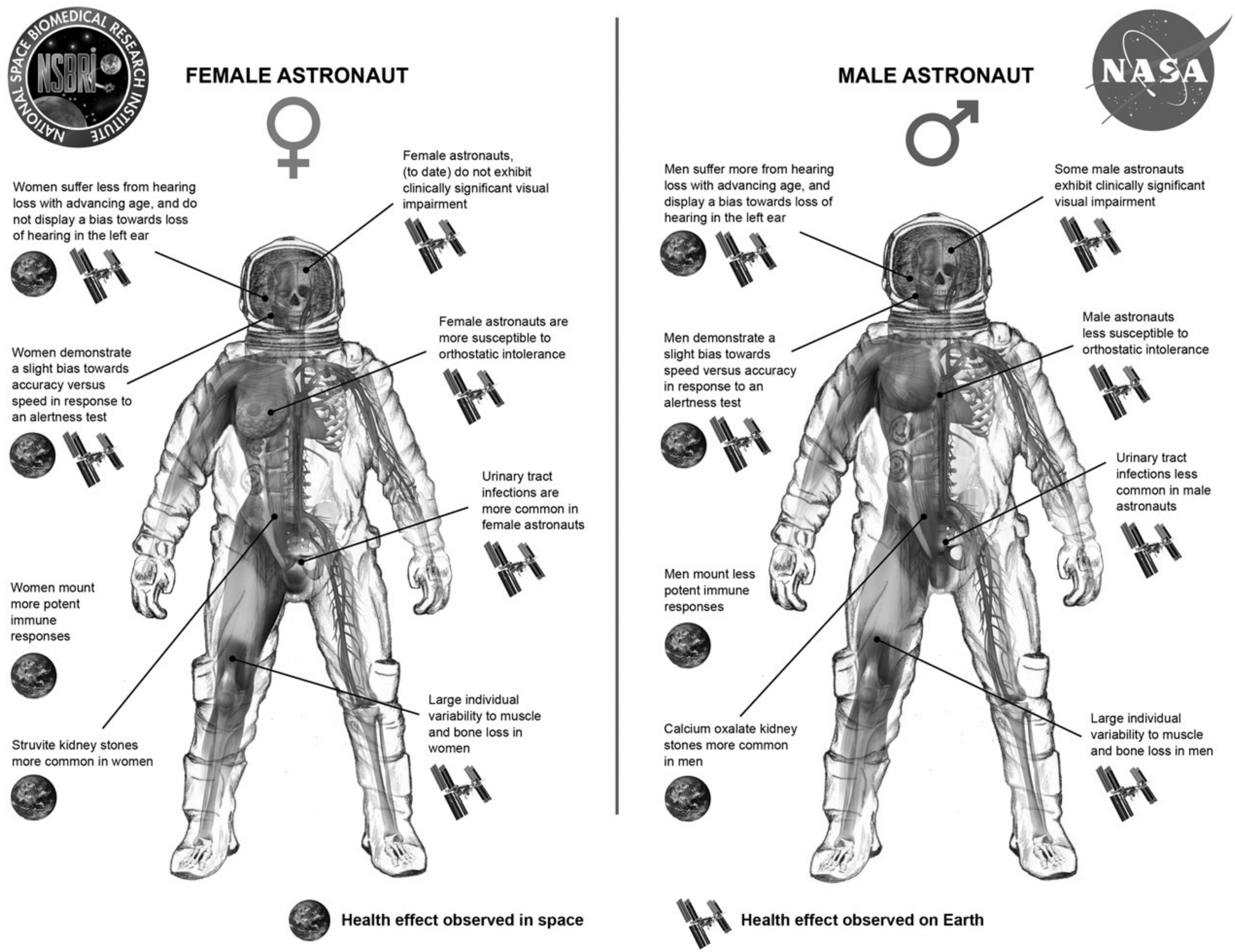

FIG. 1. Key differences between men and women in cardiovascular, immunologic, sensorimotor, musculoskeletal, and behavioral adaptations to human spaceflight.

men, including enhanced production of antibody and cell-mediated immune responses.[22,23] This makes them more resistant than men to viral and bacterial infections; and, once infected, women mount more robust responses. As a corollary, an activated immune system results in higher rates of autoimmunity; as such, over 70% of people affected by autoimmune diseases are women.[24,25] These differences may be attributed to the impact of sex hormones such as estrogen, progesterone, and testosterone on immune cell function, with each hormone having distinct effects.

Changes in function and concentration of key constituents of the immune system related to spaceflight have been reported. In addition, reactivation of latent viral antigens occurs in flight, which may persist post flight.[26–28] Accordingly, an exploration mission may increase crew risk for adverse health effects, such as infectious disease, hypersensitivities, autoimmunity, and malignancy.

Radiation represents a major hazard for space travel. Ionizing radiation deleteriously affects hematopoietic and other immune system cells.[29,30] It has been reported that female subjects are more susceptible to radiation-induced cancer than are male subjects.[31] In humans, radiation-induced breast cancer contributes to this increased risk for women.[31] Moreover, there is also an increased risk for other major types of radiation-induced cancer, such as lung cancer, in women compared with men.[31]

Sensorimotor

Men and women differ in most sensory systems, neural anatomy, and functional responses. Anatomical sex differences exist within the human brain, including a more active corpus callosum and a larger hippocampus in women and a larger amygdala in men. The sexes also differ in neuron differentiation and development and in neurochemical pathways.[32]

Sex differences in the visual senses include circular vision (orientation within a spinning environment), field dependence (perceiving orientation based only on visual cues), perception of vertical with body tilt (correctly identifying the true vertical to the ground when the body is titled), and perception of the horizon.[33,34] These differences may be due to biological differences within the vestibular system, including differences in the inner ear structures, which are significantly larger in males.[35] Men have greater sensitivity for fine detail and for rapidly moving stimuli, while women exhibit better color discrimination, possibly because many men suffer from genetically inherited color blindness.[36,37]

The sexes respond differently to stress. In rodents, stress enhances performance in males but impairs it in females.[38] The susceptibility of hippocampal cells to chronic stress has been suggested to play a role in post-traumatic stress disorder and clinical depression, which are disorders that disproportionately affect women.[39] Moreover, a brief exposure to a stressful learning situation increases the density of dendritic spines in male rats but decreases spine density in female rats.[40]

The common belief is that women are more susceptible to motion sickness on Earth; however, laboratory tests do not robustly support this assertion. Clinically, women on Earth present with more vestibular disorders such as vertigo, possibly due to the fact that they have fewer myelinated axons in the vestibular nerve than men.[41–43]

Upon transition to microgravity on space station missions, female astronauts reported a slightly higher incidence of space motion sickness (SMS) compared with men (i.e., 50% of women reported experiencing SMS versus 38% of men). Conversely, during return to Earth, male space station astronauts experience entry motion sickness symptoms more frequently (47%) than their female counterparts (40%). These differences are not statistically significant, likely due to the small sample size of the female astronauts within this dataset. These data were compiled via analysis of NASA's LSAH database.[5]

Hearing sensitivity, when measured at most frequencies, declines much more rapidly in male astronauts than it does in female astronauts. These LSAH derived data represent a wide age range of subjects (i.e., four decades) and show a more rapid decline in hearing in the left ear, for men only. Within the general population, hearing also declines more rapidly in men than in women, due in part to environmental factors or occupational exposure (e.g., construction or factory work). No evidence suggests that the sex-based hearing differences in the astronaut population are related to microgravity exposure, and the small sample size of female astronauts precludes making any definitive conclusions.[44]

Musculoskeletal

The human musculoskeletal response to unloading is highly variable among individuals, with tenfold differences often observed. For example, after 30 days of unilateral lower limb suspension in animals, individual responses in muscle loss ranged from 2.5% to a nearly 20% in plantarflexor cross-sectional area compared with before the suspension.[45] Similarly, 6 months in microgravity aboard the Mir space station resulted in a 2% to 24% loss of cancellous bone in the distal tibia.[46] These individual differences make it difficult to ascertain whether there are sex-specific effects of unloading. The initial start point for bone and muscle may influence the rate of loss with unloading in spaceflight and whether that rate of loss is linear over an approximately 3-year period, which is the approximate timeframe for current notional concepts of Mars surface missions. This is particularly germane when developing countermeasures for women and men, since men generally have greater muscle and bone mass.

On Earth, osteoarthritis of the knee is significantly more common in women than in men.[47] Sex-based risk factors include the loss of estrogen's anabolic effect on cartilage after menopause, a higher incidence of predisposing knee injuries such as anterior cruciate ligament tears, and increased joint laxity in women.[48] Since muscles serve to stabilize and dampen forces across joints,[49] loss of muscle mass and strength after prolonged unloading can contribute to joint injury risk and early degenerative joint changes, especially in the knee.

Reproductive

There are several reproductive health concerns for astronauts in space that may be primarily related to microgravity and radiation. In both populations, temporary infertility has been associated with high-dose, acute ionizing radiation exposures, as the gonads are highly sensitive to such exposures.[50] Women have a higher incidence of radiation-induced cancers, largely driven by lung, thyroid, breast and ovarian cancers, and therefore are permitted to spend significantly less time in space than men.[51] For example, a 45-year-old man has a 344-day limit versus a 187-day limit for a 45-year-old woman, due to radiation exposures on the space station that would be typical at the time of solar maximum. Theoretically, there is also more time for post-flight carcinogenesis to occur in women due to their increased longevity.

Thirteen female astronauts have given birth to 18 children following spaceflight and have not experienced any increased pregnancy complications or increased assisted reproductive technology failures compared to the general population (E. S. Baker, unpublished data). There have not been systematic follow-up health studies of the offspring. Human bed rest studies found reductions in live spermatozoa, suggesting that spermatogenesis in men may be affected by exposure to microgravity.[52]

Several hypothalamic transmitters are altered by real or simulated spaceflight. Alterations in hypothalamic pituitary gonadal and hypothalamic pituitary adrenal axes have been reported following spaceflight. Changes include reduced levels of testosterone in men[53] that appear to rebound upon return to Earth.[54] Oxytocin dampens the stress response in men and women by reducing cortisol levels.[55,56] Oral contraceptives (OC) reduce the release of oxytocin as well as cortisol.[57] Therefore, females using OCs during spaceflight may not experience increased cortisol levels and the associated stress response.

On Earth, calcium oxalate urinary tract stones are more common in Caucasian men, and struvite stones are more commonly observed in Caucasian women.[58] While no confirmed cases of urinary tract stones have been reported in the U.S. space program during spaceflight, male and female astronauts have experienced stones post flight. There is an increased incidence of spaceflight-associated dehydration and hypercalciuria, thereby increasing the risk of calcium oxalate stones in both female and male astronauts.[59]

While the overall incidence is not much different from that found on Earth, urinary tract infections in space are more common in women and have been successfully treated with antibiotics.[60] Transient difficulties with urination are reported by both sexes, but the only astronauts requiring catheterization have been women. Possible explanations include differences in hydration, adjustment to voiding in microgravity, and use of antiemetics.

Regarding conception, reptilian eggs have been successfully fertilized during spaceflight;[61] however, only one mating experiment in mice has been conducted in spaceflight and there were no viable offspring.[62]

Behavioral

Analysis of space station astronaut neurobehavioral and sleep measures showed no sex or gender differences in alertness using the Psychomotor Vigilance Test.[63] Similarly, no significant sex differences have been identified thus far using self-ratings of workload, tiredness and stress, or sleep quality in-flight or post-flight (D. F. Dinges, personal communication, 2013).

Ground-based research on sleep and circadian rhythms suggests that men gain significantly more weight than women during chronic sleep restriction.[64] Furthermore, chronic sleep restriction may induce greater increases in leptin,[65] as well as greater cellular immune activation of interleukin-6 and tumor necrosis factor-alpha in women than men.[66]

On Earth, anxiety and major depressive disorders are about twice as common in women than in men.[67] Symptoms, diagnoses, comorbidities, and responses to treatment differ for men and women.[58,68–70] There is no evidence that female astronauts experience the same risk for depressive and anxiety disorders as their counterparts in the general population. Because all astronaut candidates undergo a robust process of psychological screening and selection, the likelihood of sex differences in affective disorders may be reduced.

Conclusions

Informed decision-making regarding risks, countermeasures, and medical treatments for long-duration exploration missions requires a more thorough understanding of sex and gender differences in adaptation. Many questions remain unanswered. For example, to date, the more clinically significant cases of spaceflight-induced visual impairment have been observed only in male astronauts, but the sample size of long-duration female astronauts is still relatively modest. Conversely, orthostatic intolerance manifests more frequently in women. There may be individual and sex differences—regarding hormone, stress, and immune responses, the sensory system, and the circadian system—that are important to understand for planning exploration-class missions and designing spacecraft. These factors also influence how astronauts will safely and productively live and work in space.

Interdependencies exist between the six physiological areas that have been discussed in this analysis. The development of appropriate and effective countermeasures will require an integrated approach. Radiation, for instance, represents a harsh element of the space environment meriting more comprehensive research; for this analysis, it was thoroughly reviewed only in the areas of reproduction and immunology.

With regard to the recommendations detailed in the 2002 report, NASA has made some progress. LSAH and LSDA serve as repositories and resources for applied and clinical studies for the research community and were utilized by the six workgroups throughout this investigation. Increasingly, the design and execution of experiments funded by NASA and NSBRI have considered sex and gender in subject selection and data analyses. Inevitably, space research involves small numbers of test subjects. Current NASA and NSBRI research announcements provide guidance regarding the appropriate statistical handling of this special research challenge. In the latest crew selection, NASA selected eight astronauts, comprising four women and four men. This is a positive step toward increasing the participation of female astronauts in spaceflight and experimentation.

This analysis has heavily focused on sex differences because the data currently available have been amenable to such an approach. In the future, sex and gender differences will constitute increasingly important components of an overall personalized medicine approach to protecting the health of humans on Earth and in space.

Recommendations

- Select more female astronauts for space missions.
- Encourage and facilitate the participation of more female and male subjects in both ground and flight research studies.

- Focus on the responses of individual astronauts to spaceflight and return to Earth.
- Determine the range of effectiveness of specific countermeasures for individuals.
- Include sex and gender factors into the design of human spaceflight experiments.
- Incorporate sex and gender and other individual risk factors into NASA-funded research programs.

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