

Research Article

Bio-Medical Research on Response to Spaceflight for Emerging Civilian and Commercial Sectors in Cislunar Space, Mars and Beyond

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Citation: Rappaport MB, et al. Bio-Medical Research on Response to Spaceflight for Emerging Civilian and Commercial Sectors in Cislunar Space, Mars and Beyond. J Neuro Onco Res. 2024;4(2):1-14.

<https://doi.org/10.46889/JNOR.2024.4205>

Received Date: 14-05-2024

Accepted Date: 23-06-2024

Published Date: 30-06-2024



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Abstract

This review introduces an emerging commercial sector in cislunar space, which will soon extend to Mars, the asteroids and the moons of Jupiter and Saturn. Businesses will join state programs and provide opportunities for physicians and biomedical researchers to analyze data on the human body in space. With new capabilities at hand and with a concern for fairness, personal health and the goal of mission completion, physicians will be able to advise space travelers of their specific risks in microgravity. This review summarizes two lines of research, one very large and the other more limited. However, both will prove fruitful in preparing the larger numbers of civilians soon to enter space. Open access data available from the new Space Omics Medical Atlas (SOMA) will suggest remediations for specific groups, genders and risk profiles. Smaller studies will continue on the overall genetic and hormonal foundations of neuroplasticity in space, now in animal models and hopefully soon in humans. Of interest are the special abilities of the human species to adapt neurologically to a wide variety of environments, including exoplanets in other star systems. Here, existing remediations are summarized and experimental remediations for the future, described.

Keywords: Cislunar; Commercial Space; Space Medicine; Deconditioning; Space Genomics; Space Omics Medical Atlas (SOMA); Remediation; Neuroplasticity; Dopamine, Serotonin

On the Cusp of Another Revolution: Challenges and Opportunities for Bio-Medicine

In November 2022, the White House Office of Science and Technology Policy published the first National Cislunar Science and Technology Strategy to address “how U.S. SandT leadership will support responsible, peaceful and sustainable exploration and use of Cislunar space-the large region of space in the Earth-Moon system beyond geosynchronous (GEO orbit, including the Moon by all space-faring nations and entitles” [1,2]. The strategy emphasizes a strong and responsible American space enterprise, including exploration, science and sustainability. These are indeed the themes that have emerged in the last decades of discussion, publication and debate, for example, in The Human Factor in the Settlement of the Moon, published in 2021, a volume that repeatedly integrates off-world environmental goals in each chapter, especially on Earth’s Moon [3].

The health and welfare of all spacefarers depend in many ways on the environmental commitments of space exploration and now, space commerce. Commercialism is set to emerge rapidly and to take on important functions alongside off-world scientific research, evaluation and testing. In 2024, U.S. Space Force published its “Commercial Space Strategy” whose Foreword summarizes the change in space activities this way: “The nation and the world have seen a renaissance in space with unprecedented innovation emerging in commercial and allied space systems in the past decade.” Their goal is stated here: “In this increasingly congested and contested space domain, we must seize the opportunity to capitalize on significant innovative

commercial space solutions” [4]. There will be opportunities for physicians and bio-medical researchers to join an increasingly complex set of off-world programs, both commercial and governmental, to keep crew and visitors safe and healthy and to join in the development of a specialized lunar space medicine.

As on Earth, the pursuit of business interests will both vie with and join with, the programs to keep spacefarers healthy. Space medicine will continue to emerge as a centrally important medical discipline from now, on, into a future that includes interstellar exploration.

Social Forces Impacting Cislunar Space, Mars, the Asteroids and Beyond

The U.S. National Aeronautics and Space Administration (NASA) plans for the International Space Station (ISS) to be decommissioned probably in the year 2030. Microgravity research and technical development will be continued actively to the end. At the same time, NASA is working to help new, Low Earth Orbit (LEO) stations to be in place by the time the ISS leaves orbit and falls to Earth in a controlled manner into a non-populated area—a maneuver planned by NASA, ESA (European Space Agency), JAXA (Japan Aerospace Exploration Agency) and the State Space Corporation Roscosmos. This group of international agencies has managed the ISS since 1998 [5,6].

When NASA replaces the ISS, it plans to purchase services rather than conduct its own programs changing the manner in which research, including medical research, is planned, approved and administered in LEO and therefore, probably how research is conducted initially on Earth’s Moon and its future Gateway orbital station around the Moon. A variety of joint commercial ventures with Earth-orbital stations such as Axiom Station, Orbital Reef, Starlab and others, will replace the ISS in a decade [7]. It is easy to interpret these changes as serving a small proportion of all humans. However, the knowledge gained and the products and devices developed in response to these early, civilian spacefaring programs will feed into development processes on Earth—in part, through the work of physicians, biomedical researchers and other scientists. Figure 1 outlines some of the most important domains for development: Research; International Program Development; and Commercial Expansion. These are not the only domains in LEO or in the remainder of cislunar space. Facilities can serve human needs as diverse as art, religion and recreation. Still, space-generated knowledge and applications stand as one of the most productive lines of technical development for all nations on Earth. The timelines can be lengthy and the routes of influence sometimes difficult to trace, but in the end, all humans on Earth will benefit from early programs in cislunar space. To term these developments a “revolution” for the human population on Earth is no exaggeration because many materials, technologies and much scientific knowledge would not be generated and distributed without early programs developed in and for cislunar space.

From one perspective, the retirement of the International Space Station around 2030 represents the beginning of an important change in the exportation of human civilization off our planet. It moves space programming from largely nation-based programs to commercial efforts and thereby ensures that practicality and profitability will be very important factors in the survival of off-Earth settlements. Business motives and standard operating procedures will come to characterize the administration, management protocols and equipment of stations in cislunar space and in transit to and from Earth’s Moon. A larger and more varied population of humans will have experience in space and others will learn from them. NASA’s Artemis Accords, noted in Fig. 1, appear in full in Note 1, below and they help to set international standards for communication, transportation and other fundamental types of coordination and cooperation necessary among Earth’s nations.

The phrase “population of outer space” will change in meaning. For that new population, it will be possible to record research results on each new spacefarer by using implants and other devices to gather data on physiological and neurological deconditioning in space—if they allow it. It is hoped that new space platforms will build into their administrative requirements participation in a myriad of research programs. While participation will not be everyone’s preference, many will be motivated to contribute information on their own body in space. It will be an intrusion, but an opportunity to contribute. Collection and analysis of genome and physiological data in space mean that future settlement programs can proceed more deliberately and developers will know more about the requirements of the human species in lower gravities.

A new era is unofficially marked by the decommissioning of NASA’s International Space Station and its replacement by private orbital stations. Over the coming years, it will become obvious that the human risks in spaceflight will be clarifying for centuries.

Different forces are at play, for example, progress in engineering research that provides ever-more-available means to experience artificial gravity, for at least short periods of time. That exposure may counteract some deconditioning in spaceflight.



Figure 1: Social and economic forces impacting cislunar space policy. (The Artemis Accords in 2., above, appear in Note 1).

A Second Space Age Spanning Omics, Platforms and Medicine Across Orbits

Deconditioning in spaceflight is not yet fully understood and research agendas will grow and change in coming years. One major recent research thrust emerged from work on the NASA Twins Study [8] and this field is now referred to as, “Genomics in Space” or “Space Omics”. It was marked recently by publication of an open access capability, The Space Omics and Medical Atlas (SOMA) and international astronaut biobank [9]. A parallel publication in the journal Nature, “A Second Space Age Spanning Omics, Platforms and Medicine Across Orbits” was headed by Christopher E. Mason of Weill Cornell Medicine, who led of 70 co-authoring scientists. Their affiliations illustrate breadth of research venues involved in assembly of the data in the Atlas and development of analytic approaches to the data-which is a field unto its own. Use of the Atlas relies especially on the capabilities of molecular biology and precision medicine for space crew. Those efforts will eventually enable the identification of an individual’s risk factors and potential remediations. The collection of data is strongly international, bringing together results from JAXA studies, as well as studies on Inspiron4 mission crew members and NASA and ESA astronaut crews. Table 1 provides a summary of the current state of remediations available now and potentially available in the future. Research may change this list substantially in coming years, as, for example, CRISPR techniques allow the insertion of capacities to alleviate many of the discomforts, problems and maladaptations encountered to date by spacefarers.

Deconditioning Factors	Deterioration Results	Current Remediations	Future Developments
Microgravity	Physiological and neurological issues and activity	Staying fit with a specialized diet, exercise, adequate sleep and vitamin supplements	Artificial gravity for periods or constant application
Ionizing Radiation	Breakage in DNA strands affecting, for example, cancer outcomes	Genetic statistical analysis to highlight more susceptible crew members for monitoring	CRISPR-Cas9 gene reprogramming; active and passive radiation shielding
Environmental Control: CO ₂ Levels Temperature Humidity	Lowered cognitive performance, labored breathing, eventual loss of consciousness	Monitoring of environment and of crew's cognitive performance	Refining computerized adaptive testing; incorporating AI to aid crew in autonomous operation of systems
Cramped Quarters	Increased stress from lack of privacy	Attention to, for example, hygiene areas and choice of color schemes	Decreasing stress response via genetic therapies
Separation from Family and Friends	Increased isolation as Earth gets smaller	Social robots; conversational AI therapists	Nanoparticle precision drug delivery
Pressure of Daily Tasks	Increased mental and physical fatigue	Systems approach to integrating AI with humans in their tasks	Rehabilitative neuroprosthetics

Table 1: Deconditioning factors for humans in space: current and future remediations.

Neuroplasticity in the Human Species and “Spaceflight Neuroplastic Syndrome

A more modest, but interesting and potentially important research thrust is in the field of neurology, specifically studies on neuroplasticity-the changeability of neurological features in microgravity. Early results from the work of Popova and colleagues' probe at the deepest levels of genetic and hormonal regulators (Table 2). These results appear to point to the reasons, at foundation, of neurological changes in mammals in microgravity-although let us be quick to say that this research needs to be conducted on humans, as well, to demonstrate whether the research in Table 2 is replicated.

Results from Popova, et al., [10] Cf. [11,12].	Key
“Long-term” spaceflight (about a month) affects the principal regulators of brain neuroplasticity: neurotransmitters (5-HT and DA) and neurotrophic factors (CDNF, GDNF, <i>but not</i> BDNF)	5-HT = serotonin risk-and-reward system, stored primarily in the gut, regulates mood, cognition, reward, learning, memory, sleep and stress DA = dopamine risk-and-reward system, stored in the brain, regulates locomotion, muscle tone; modulates motivation, reward-related behavior and learning. CDNF = cerebral dopamine neurotrophic factor GDNF = glial cell derived neurotrophic factor BDNF = brain derived neurotrophic factor, which has a major affect on the 5-HT system, more than the DA system
Brain response to spaceflight is region-specific. The substantia nigra, striatum and hypothalamus are highly sensitive to long-term spaceflight. In these brain areas spaceflight decreased the expression of both DA-related and neurotrophic factors genes.	
Risk “neurogenes” (genes at risk in spaceflight) include genes affecting both serotonin and dopamine pathways. 5-HT related genes are 5HT2A receptor and MAO A. DA-related genes are TH, MAO A, COMT, D1 receptor, CFNF and GDNF.	

Table 2: Results on neuroplasticity in the rodent model in microgravity.

It is hoped that results in the rodent model will point the way to appropriate, parallel research questions for human spacefarers, especially, how changes in human decision-making might occur through comparable effects in humans. While some of the neurotrophic factors have been linked to various mental health issues on Earth-and those results are useful in discussions of potential effects on humans in space-it remains true that the detailed roles and functions of all the individual types of neurotrophic factors have not been clearly delineated by research, so there is much work to do.

The various samples of rodents stayed in space for times that were considered long-lasting for that size and type of mammal. More recently, findings on immunological, hormonal and hemostasis factors were published for cosmonauts who engaged in “prolonged” space missions of up to six months, which is approaching the times for perhaps early, LEO missions or round trips to Earth’s Moon [13]. As these data emerge from widely scattered comparative studies, it is becoming increasingly clear that the theory and models to explain the body’s functioning cannot simply be labelled “adaptation to microgravity”. The explanations need to analyze why the reported changes occurred while other changes in other neurotrophic factors in the same systems, did not. It is becoming obvious that the theory of space neuroscience and how space affects mammals that evolved on Earth is just at its inception. The state of this branch of research could be characterized without too much exaggeration as “swimming in data” with little theory or models to guide conclusions that point to next steps in research and space program development.

The present authors’ interest in neuroplasticity derives from its importance in the field of anthropology and the high-level neuroplasticity seen in hominid species. Neuroplasticity’s apparent importance in spaceflight has led to our interest especially in various species of the genus *Homo* as advanced primates-including prehistoric species [14,15]. There are intriguing connections between neuroplasticity and human evolution and neuroplasticity and human development, focused on the reliance of humans on their high level of neuroplasticity for the expert use of a specific language and culture [16]. An implication is that high neuroplasticity is intimately involved with use of a biological capacity for culture. Therefore, our particular interest emerged not from spaceflight per se, but from our focus on the evolution of higher cognitive capacities in the human species [17].

The current living species of *Homo*, *Homo sapiens sapiens*, is reliant on neuroplasticity for early development, language use and there are some indications that neuroplasticity may be important for humans in spaceflight. While neuroplasticity causes some problems, it also enables some adaptation to spaceflight and there is great interest in whether and how, humans adapt to microgravity, at least to a degree-and, of course, whether this capacity can be aided or supplemented. Human neuroplasticity may also enable accommodations to a variety of gravities and conditions on other planets in our solar system and in systems around other stars.

Research on neuroplasticity in spaceflight has been primarily on rodents at genetic and hormonal levels in rats and mice, especially the dopamine and serotonin risk-and-reward systems. This connection opens the door to implications for human decision-making in space [14,15]. New programs in cislunar space (such as NASA’s Gateway orbital station planned for the Moon), early posts and settlements on Mars and mining stations on the asteroids could provide important opportunities for research on the fundamental basis of neuroplasticity, deconditioning and the identification of individual risk factors.

Our proposal of a Spaceflight Neuroplastic Syndrome is based upon both reported changes among astronauts in human fluid distribution, balance and difficulties in locomotion upon return to Earth and upon the changes summarized in Table 2 by Popova and colleagues [10,15]. In this review, the term Spaceflight Neuroplastic Syndrome is used to generally address changes in the neurological system in response to space that may appear maladaptive from a terrestrial frame of reference. Development of a refined definition will depend on good research now and in the future. A working definition of neuroplasticity is a set of biological processes that involve what appear to be “adaptive” structural and functional changes to the brain, its structure and peripheral nerves, as well as sometimes the organs that these nerves nourish.

The nature of the “adaptation” is related to the environment in which the species finds itself, so that what appears adaptive on Earth may not be adaptive in space and vice versa. In general, neuroplasticity was recognized early as a general marshaling of restorative processes of the nervous system. Most species have juvenile neuroplasticity that is gradually lost with adulthood. However, there remain different ways to access immature neurons in adults of different species, so that access to neuroplasticity is not completely lost among adult animals. In comparison to many animals, humans are seen to have rather high levels of neuroplasticity. This can be advantageous or a problem if the human is in a space environment.

The Importance of Neuroplasticity in a Social and Economic Context

Space stations and other facilities at the level of Low Earth Orbit usually have something over eleven orbits per day and they circle the Earth at a level of around 2000 km or 1200 miles from the planet [18]. Once the technical, managerial and safety issues of boosting large numbers of humans to that orbital level are developed and implemented and safety is assured to a reasonable

extent, it is likely that an increasing number and variety of individuals will want to experience space for a wide variety of reasons: scientific, humanistic (philosophy, journalism), artistic (graphic, sculpture, photography and musical arts to name a few), exploration by youth and adults who belong to travel, sports and adventure clubs and even spiritual reasons pursued in programs hosted by religious organizations. None of these motivations to experience space is unreasonable for future civilian spacefarers. Still, they require a clear understanding of the physical, cognitive and emotional challenges for civilian spacefarers who are not rigorously trained, as astronauts were, so that their needs in Low Earth Orbit can be met.

There is understandable excitement and motivation for profit. Humans will explore the Earth and Moon, the lunar surface, Mars, the asteroids and the “ocean moons” of the outer planets. Given worldwide trends and the status of spaceflight research, a synthesis has arisen whereby basic research will continue on the nature of neuroplasticity, proposed as the underlying cause of some aspects of deconditioning.

This review is intended to encourage creative thought about research on human spaceflight and remediation for the difficulties it causes the human body and mind. Given the research results and theory on neuroplasticity presented here and the broader societal needs for the economic development of space, there is great need for development of space medicine. Intriguing research in the rodent model suggests spaceflight causes changes down to the genetic and hormonal levels. Before results are understood better, civilians will enter space according to cost-effective approaches that include genetic testing, genomic analysis, diet, exercise and knowledge of the risks of a specific off-world venue.

A deeper understanding of human neuroplasticity can potentially aid physicians and health care workers provide advice to humans who venture into space for the first time. Activities of world populations will soon involve the use of Earth’s skies for work and recreation, as well as research. Low Earth Orbit will be as accessible to many people as their next, rather distant vacation spot on Earth. The dangers of neurological de-conditioning remain and they await to be addressed through both preparation and remediation and used for the advantages that human neuroplasticity offers humans naturally in the area of adaptation to an environment.

Development of Space Neuroscience: Theory in a “Sea of Data”

Human expansion off Earth entails the emergence of a new scientific understanding of changes to the human body produced by the environment of microgravity, higher concentrations of CO₂ and high levels of cosmic radiation. Humans and other terrestrial organisms did not evolve to be adapted to those conditions. Nevertheless, there is some evidence that the mammalian response is one of adaptation that in some ways succeeds, while in other ways it fails. This is a conclusion that has evolved over the past decade and a half, using different terms and theoretical contexts [10,15,19-23].

This review explores some of the implications of a relatively undeveloped space neuroscience in the very early years of off-Earth human expansion. Recent findings on neuroplasticity join findings among early astronauts, like vestibular changes and disturbances in balance [24]. There is also increasing coverage in the literature of physiological changes wrought by microgravity in the immunologic and hemostasis systems [13]. An examination of all these observations points to a need for improved theoretical development.

To some recent authors, it appears there is much data but a deficiency of theoretical models to organize them. This appears to be an apt observation for the more specialized field of space neuroscience. While there are a few excellent, early studies, there is a paucity of theoretical models to help explain the data from early spaceflights, few models as to why certain changes occur but others do not [14,15]. It should be noted that this deficiency does not characterize neuroscience alone, but other scientific fields as well. It is noteworthy that the very recent neuroscience literature supports this interpretation of the state of theory and that this is consistent with theory on humans in space. Horatio Rotstein of Rutgers University and Fidel Santamaria of University of Texas at San Antonio frame the issue in an online paper as one of “Development of theoretical frameworks in neuroscience: a pressing need in a sea of data” [25]. Like other sciences, data collection in neuroscience out-paced theory and modelling, partly because of the availability of technical instrumentation to gather the data. These are not the only branches of science that will find themselves confronting large quantities of information and struggling to organize it, store it and model it-in some cases without much help from theory and conversely, not very productive of theory.

To grapple with this issue, Levenstein and colleagues approach neuroscience in a practical way, i.e., by focusing on theory that is meant to solve specific problems [26]. However, they also take the reader through careful steps of abstraction and interpretation and they include a useful discussion of the role of models in connecting theory and experiment. Finally, an analysis by Goss recommends in the title, “Build It and the Science Will Come”, which is both a good suggestion and a pragmatic approach for space science, especially when risk calculations allow it or need is pressing [27]. This last suggestion reflects the present situation in terms of theoretical explanations for the neurological effects of what we call Spaceflight Neuroplastic Syndrome, especially the effects of space on neurotrophic factors and neurotransmitters and the potential for subsequent effects on human decisions.

The placement of mammalian decision-making within a sufficiently deep and broad theoretical framework will be difficult, especially for human decision-making, where complex decision-making occurs at genetic, synaptic, hormonal, organ, network, behavioral and group levels. None of those levels is fully researched or well understood yet, although there is much hope for the future in works by Schultz, Calder, Aerts, Collins and Shenhav and their colleagues internationally, for good modeling of decision-making in neuroscience [28-31].

Regulators of Neuroplasticity and Development of Theory

Using findings from a variety of experiments on different spaceflights, Popova and colleagues discovered that experience in space affects some of the principal regulators of brain neuroplasticity in the rodent model [10]. Neurotransmitters serotonin (5-HT) and Dopamine (DA) and neurotrophic factors Cerebral Dopamine Neurotrophic Factor (CDNF) and Glial Cell Derived Neurotrophic Factor (GDNF) are indeed affected by spaceflight. CDNF and GDNF are strongly nurturant of the dopamine system. The question remains: Does spaceflight affect the functions of dopamine in humans and if so, which ones? Decision-making is surely not the only function relying on dopamine.

Neurotrophic Brain Derived Neurotrophic Factor (BDNF) is not affected by spaceflight and is strongly nurturant of the serotonin system [10]. The question remains: Is this an advantage for humans and does BDNF's stability in space offer any advantage? Most of the serotonin (5-HT) is stored in the gut with roughly 2% being produced in the brain. Serotonin regulates mood, cognition, reward, learning, memory, sleep and stress. DA is stored in the brain and regulates locomotion and muscle tone and it is connected to reward, aversion, decision-making and learning. All neurotrophic factors have a role in neuronal development, function and the survival and plasticity of mature neurons. They are foundational to humans' high level of neuroplasticity and by implication, to their profound ability to make decisions, especially in groups.

Findings and Unknowns on the Neuroscience of Human Decision-Making in Space

“Long-lasting” space travel (around a month) in the rodent model produced significant changes in genetic control of dopamine and serotonin circuits. It is probable that some comparable changes occur in humans in spaceflight but it is not yet clear whether they would affect human decision-making in space. While there is a variety of changes in some “risk neurogenes” and neurotropic factors in spaceflight [11], it is not yet clear whether they adversely affect decision-making even for rodents and if they do-how. Some changes could be compensatory or adaptive relative to a space environment and they could support decision-making in spaceflight. Follow-up research should clarify whether and how changes in neurotransmitters and neurotrophic factors function in decision-making during human spaceflight. Answers may be complex, detailed and varied because to date there is little report of fundamental problems for humans who need to make simple or even complex decisions in space. A further and possibly even more complex research question is: what imparts human stability in decision-making? Is BDNF involved?

Also undetermined at this point is whether and to what extent, changes in spaceflight affect decision-making at different levels of complexity-from simple task decisions to complex group decision-making. It may be that some of the neurological foundations of decision-making that change in spaceflight are ones for which other levels of human decision-making can compensate. Until definitions of all the levels of decision-making are refined and research on them is conducted and connected, it will be difficult to know for sure. The connections between levels of human decision-making - genetic, synaptic, hormonal, organ, network, behavioral and group levels - are not yet well researched on Earth in full gravity, much less in a space environment of microgravity, heightened CO₂ and higher cosmic radiation. Scientists will try to understand human physiological changes in space using rodent and eventually human findings, but at this point, it remains unclear how long-lasting the changes in the foundations of decision-making remain and whether there is any acclimatization to space by rodents or humans with respect to

neurotransmitters and neurotrophic factors [15]. It is unknown how “recovery” from space proceeds in space or on Earth.

There are several suggestions that recovery begins in space after neurological deconditioning, as a type of “adaptive plasticity” or what a biologist might term “phenotypic adaptation” [32]. There are suggestions in some research results that “focused activity” might be able to counteract some neurological changes [33]. Similarly, the results of Scully and colleagues’ work suggest that well trained individuals in good health (like astronauts) might be able to counteract some of the effects of deconditioning and continue to perform and make decisions at a high level of effectiveness subject to what is elsewhere called the “overcoming effect” [15,34]. Finally, there are potential remediation efforts using gravity and others that do not use gravity, which may counteract some of the most difficult aspects of neurological deconditioning and they are summarized here in Table 1 and described elsewhere [14,15].

One can begin to understand the research benefits when larger numbers of civilians begin to populate LEO on various space stations and in new orbiting facilities-even hotels, hospitals and convalescent facilities. Research on participants and on the efforts to counteract the neurological symptoms of Spaceflight Neuroplastic Syndrome should provide excellent data for space medicine. That knowledge will help to plan future programs in cislunar space.

Reported changes in “risk neurogenes” and neurotrophic factors, to date, are the most deeply seated changes that have been identified - down to the hormonal and genetic levels [10,11]. These are joined by other, more recent results on immunological and hemostasis changes [13].

It will be eventually a race to discover the most important consequences that could affect work performance in upcoming space missions once the economic consequences are realized and actualized. With plans already in place to begin to settle the Moon and Mars, these questions about human neurological deconditioning should be placed high on a list of research priorities. While the question might appear contrary- even argumentative- it will be extremely interesting to discover why the sequelae of spaceflight for humans have not, to date, been worse, given the widespread character of changes in neurotransmitters and neurotrophic factors in the rat model. This question has not been broached in a systematic manner and there are few suggested answers in the literature, except perhaps that the high level of neuroplasticity in humans may in fact offer some benefits, as well as the noted deficits [14,15]. It would not be unusual for humans’ high level of neuroplasticity to cause diverse and even conflicting responses. Human neuroplasticity may indeed have its “upside”.

Future Research on Decision-Making in Space

Comparative Studies Yield New Insights on Neuroplasticity

Research on neuroplasticity among animals is changing, along with a growing number of comparative studies of invertebrates, vertebrates, non-mammals and mammals. Results suggest that there are different origins of adult neuroplasticity, i.e., capacities to produce new neurons in adults [35]. Some are produced from stem cells in adulthood. This capacity to produce new neurons in adulthood is widespread in non-mammalian vertebrates but not widespread in mammals. The review by Bonfanti and colleagues reports on an alternative source of adult neuroplasticity in large-brained mammals who have many neurons with markers of neurogenesis, but no cell division and maturation. These researchers explain that Layer II of the cerebral cortex has prenatally derived, but non-dividing neurons that continue to show immaturity throughout life. Those neurons may serve as a source of neuroplasticity for adults. The authors’ hypothesis is that there could be an evolutionary trade-off between different “reservoirs” of mature neurons and therefore neuroplasticity, during the lifetimes of different types of animals. Comparative analyses show that there is substantial variety in the origins of mature neurons in adulthood [35]. Among primates, as a group, there is a variety of means to maintain neuroplasticity into adulthood.

Whatever the source of mature neurons in the higher primates, zoologist David Begun is correct in noting: “It is undeniable that primates prioritize cognition and behavior flexibility over genetically determined behavior” [36]. Indeed, the higher neurocognitive capacities of the hominoids appear to rely on whatever biological source of mature neurons may exist for each species. Neuroplasticity is one of a variety of types of plasticity that characterize the higher primates. In spite of early reports of serious difficulties concerning neuroplasticity in human spacefarers, it remains an extraordinarily useful quality for humans as they stand on the cusp of a major change in environment-the microgravity of space and the lower gravity of off-Earth planetoids

that may serve as new homes. In fact, humans may someday need to adapt to the higher gravity of an exoplanet circling another star.

Research Questions on Decision-Making in Space

At this juncture, at the beginning of a new spacefaring age, Schultz' reminder about biological reward systems bears repeating: "Rewards are the most crucial objects for life. Their function is to make us eat, drink and mate. Species with brains that allow them to get better rewards will win in evolution. This is what our brain does, acquire rewards ... and in the best possible way. It may well be the reason why brains have evolved" [28]. It is true that rewards have become much more complex for the human species and choices are guided by a multiplicity of motivations. Nevertheless, the foundational systems for reward, choice and decision-making remain in place. They are characterized by very specific changes in space, as we have seen (Table 2).

Early studies of mammalian decision-making in space focus on changes in the foundations of decision-making, i.e., in the risk-and-reward systems based on dopamine and serotonin [15]. A model for human decision-making in space will hopefully emerge in part from modelling data on the dopamine and serotonin systems' neurotrophic factors and neurotransmitters in the rodent model from research by Popova and colleagues and by others in the future [10-12].

To even the casual reader, the following questions leap out of their work, without good answers yet:

First, does the identified pattern of changes in involved regions of the brain, for example, the prefrontal cortex, substantia nigra, striatum and hypothalamus according to Popova and colleagues [10], impact decision-making in space-even in the rodent model? At the present time, it is not yet possible to confirm the thesis that changes in comparable human neurotrophic factors and neurotransmitters affect human decision-making in spaceflight. They may do so and some would say, they probably do, at least minimally, but no one knows for sure and it remains an unsolved issue.

Second, if changes in neural components affect human decision-making in space, can the changes be "overcome" by special human qualities such as agency, focus, perseverance, flexibility and ability to make decisions in groups? Are humans perhaps simply fortunate that not all neurotrophic factors and neurotransmitters are affected by spaceflight-if this turns out to be true? If so, then it may make less difference that some of these neural components supporting dopamine and serotonin change during spaceflight. Early work by Scully supports this line of reasoning in "astronaut-like" human subjects [34].

Third, why are some of the neurotrophic factors that nourish dopamine and serotonin systems affected by spaceflight and others not affected? Can this point the way toward remediation or even preparation for spaceflight by humans? To discover that there are steps that civilians can take to minimize the effects of Spaceflight Neuroplastic Syndrome would surely be advantageous for program development in cislunar space and in the one-sixth gravity of the Moon's lunar surface [15].

Fourth, the complexity of explaining human decision-making in space derives directly from the complexity of human decision-making itself, which emerges at around three or four years of age and remains effective through adulthood. Even at the young ages of three and four, the human group-process is far superior to that of the monkey and ape [37]. Children at that age "work it out" using trial-and-error and verbalizations and arrive at a group solution.

All these questions on the state of space research could have implications for the health, wellbeing and occupational effectiveness of civilians in space. Many research questions in space neuroscience are unanswered today and they will remain unanswered in the early decades of off-Earth experience by individuals who are not as rigorously trained or in as prime condition as astronauts and cosmonauts have been in the past.

When examining rodent vs. human models, it should be remembered that there is an enormous difference between the two sets of mammals in that humans routinely use group-process decision-making. On most space missions, group decision-making involves both crew in space and mission control staff on Earth with whom the crew communicate regularly to make decisions. Humans are perhaps uniquely gifted in being able to group-process decisions without necessarily having teammates in the same room (or on the same planetoid).

While a great deal has been learned about the ways that biological systems change in response to the entirely new environment of space, there is still a great deal to be discovered at the genetic and hormonal levels of mammalian decision-making systems. Equally important is an understanding of the intense and complex sociocultural decision-making that takes place in and between, all members of human groups, whether on Earth or in space.

On Earth, the human species is known for its singular group-process skills continue to blossom from childhood through adulthood among humans, often into a senescence that lengthened during human evolution. Group process is bolstered by a type of flexibility with language and other symbolic communication modes, like mathematics and geographic wayfinding that expanded to three dimensions.

It will be important for space medicine to mediate neuroplasticity and “harness” it, if this can maintain the effectiveness of crew in space [38]. Researchers will find essential an understanding of whether changes at the genetic and hormonal levels change decision-making abilities at both the individual and group levels. It will be necessary to comprehend decision-making at the individual level when crew members are multi-tasking on space missions. While some research on basic decision-making tasks has been accomplished, for example [39,40,34,41], there is very little information other than anecdotal on how group decision-making occurs during a space mission in LEO, on brief missions to the Moon and back and in the rest of cislunar space.

Insights on Neuroplasticity from Hominid Evolution

In combination with emerging archaeological pictures of the behavior of early modern humans and how prehistoric species of hominids varied, neuroplasticity became a key indicator related to varying capacities for culture, learning and language in early modern humans, Neanderthals and Denisovans. Once these varieties of human were genetically sequenced, scientists focused on the genetic variants, FOXP2 (known to be related to a modern speech disability) and SRGAP2C, which is involved in growth of the cerebrum. The FOXP2 gene directs production of the protein named, forkhead box P2, which is likely essential for normal speech development in modern humans. Gómez-Robles and Sherwood diagram the distribution of different types of FOXP2 gene variants - some, coding genes and some regulatory genes [16]. Modern humans have human variants in both coding and regulatory genes. However, Neanderthals also have the modern human form of the FOXP2 coding gene, but a non-modern form of the regulatory gene variant. The Denisovans have the human coding variant of FOXP2, but the non-human regulatory form of FOXP2. These three early hominids are different in the gene distributions of important foundations of language ability.

At the same time, researchers of the prehistoric sites of early modern humans, Neanderthals and Denisovans began to see behavioral differences that they could link to flexibility in speaking and thinking. For example, Neanderthals apparently did not have a three-dimensional grid in their cognitive wayfinding skills [42]. They returned directly to base camp time and time again in a star pattern, which took them from the center, outwards and back, multiple times. On the other hand, early humans “cut the corner,” going out from center to periphery and then, going on to another peripheral point without going back into the center of the encampment immediately, but eventually finding their way to the center via a different route. The latter shortens the distance traveled and sometimes, one can presume, allows heading off prey or competitors.

Neuroplasticity began to be associated with a general flexibility of behavior and thought among the higher primates, especially hominids and especially one of them (*Homo sapiens*). Let us look at the SRGAP2C gene, which has a role in migration and differentiation of neurons contributing to the brain cortex [43,44]. Gómez-Robles and Sherwood examined the distribution of SRGAP2C among the same higher hominids and found that all of them - modern humans, Neanderthals and Denisovans - have the same “human” variant of SRGAP2C [16]. The difference in these three higher hominids is in the regulatory FOXP2 variant. Modern humans have the human regulatory form, but Neanderthals and Denisovans have the “nonhuman” regulatory form. This differentiation in regulatory genes that sets apart higher forms of primates, is not unusual and characterizes other features at the foundation of higher-level cognition and behavior.

Clearly, if there were variants of SRGAP2C that differentiated degree or pace of migration of neurons to the cerebral cortex of these three higher hominids, that variant of SRGAP2C appeared earlier and was replaced by the human variant of SRGAP2C. Now, it characterizes all three higher hominids from earlier forms. Relatively speaking, the three species are in many ways very much the same, but only one survived to the modern era, *Homo sapiens*. The biological classifications of the other two species

vary among analysts according to the newest findings. They are all “hominoids”, which include humans, ancestral human forms and anthropoid apes.

Therefore, one can ask if the differentiating gene variant, the regulatory FOXP2 gene variant, has some special connection to language and culture learning, as well as both cognitive flexibility and flexibility of response to external stimuli. As one examines genetic differences among early hominids at various archaeological sites, one is struck by how often it is the regulatory form of a gene that distinguishes the higher species. The coding genes often remain the same, but the regulatory forms change and often appear to make substantial differences. From the perspective of genetic evolutionary change, changing the regulatory gene could be an efficient way to create new species traits: modern language, modern wayfinding and flexibility in mind and body - those qualities that will become so useful as humans experience spaceflight and explore new worlds.

A Possible Proxy Measure for Neuroplasticity: Helpful or Exclusionary?

Useful indicators can be determined by questionnaires and health histories, but medical testing will be preferable for some of the most important risk factors. It is possible that level of BDNF could be used as a measure obtained rather routinely from the human gut and therefore serve as a proxy for neuroplasticity and changes in it. Recall that 5-HT is stored in the gut and regulates mood, cognition, reward, learning, memory, sleep and stress. Indeed, there is research that depression, neuronal loss and cortical atrophy are related to lower levels of BDNF. Martinowich and colleagues find that a return of normal levels of BDNF is linked to antidepressants and Arosio and others explore some of the issues for use of BDNF as a biomarker [45-47].

If a proxy measure is then used in a way that depression becomes a selection factor, allowing some civilians in space and not others, then it becomes obvious just how problematic this might be. Indeed, this is but one example of allowing some civilians to experience space, but not others, based on some disadvantageous factor such as depression. The entire issue of exclusionary measures will need careful consideration in the decades upcoming. Measures of neuroplasticity, their changes and their natural sequelae cannot become exclusionary beyond reasonable limits. And yet they could prove useful when large numbers of civilians want to experience space in this early stage of off-world exploration. The pools of people from which astronauts have been selected are extremely well researched. Often these are members of the military or some other government unit who were accustomed to having a degree of their privacy taken away. Civilians may not be so willing to relinquish private details of their medical histories.

Conclusion

“Being There”: Research, with all its methods, ethics and procedures, is one of the most important of all human enterprises to extend off-world. It forms a foundation for civilization wherever it has arisen in the past and wherever it exists now, because research is based on objective, repeatable collection of information that can be used for decision-making. The export of research has technically already occurred in experiments with animals and plants in previous and existing space stations. In the following decades, it will occur more extensively in cislunar space, while older space stations are destroyed or renewed and new and larger space stations, built. Research will necessarily occur in the first permanent settlements on Earth’s Moon, while monitors and tracking systems follow the health of the first settlers. Research will be found in orbital stations around the Moon, like Gateway and its descendants and in the gravitationally stable Lagrange points where mammoth spaceships will likely be assembled and parked until use. Elsewhere, these two authors and a wrote in 2022 of the future of research in microgravity, after the transition of the International Space Station to civilian hands. We first noted the importance of “being there”-for humans to live, even for a short while, in LEO and conduct research there. Research questions will be asked and new approaches will be developed that could not be anticipated and envisioned on Earth. Protocols for collection, transmittal and archiving of data will be created on site, in space, in response to research needs that scientists, administrators and humanists cannot envision fully until they are in space and need of new methodological approaches. The environment of cislunar space will create both needs and capacities, as it has in every environment on Earth.

Note

Note 1. The Artemis Accords (in brief).

Peaceful Exploration of space: Nations agree that all activities conducted under the Artemis program must be carried out for peaceful purposes in accordance with international law.

Transparency: Signatory nations should conduct their activities in a transparent way in the hope this prevents both confusion and conflict. This also extends to signatories sharing scientific information with the public and the international scientific community on a good-faith basis.

Interoperability: The accords say that nations participating in the Artemis program should aim to develop and provide support for systems that can work in conjunction with existing infrastructure, hopefully enhancing both the safety of space operations and the sustainability of these missions.

Emergency Assistance: Nations signing the Artemis Accords are committed to assisting astronauts and personnel in outer space who are in distress.

Registration of Space Objects: Nations participating in Artemis should determine which of them should register any relevant space object.

Preserving Heritage: Artemis Accords signatories have committed to preserving humanity's outer space heritage. This includes sites with historic significance such as human or robotic landing sites, artifacts, spacecraft and other evidence of activity on other celestial bodies.

Space Resources: The accord signatories affirm that extracting and utilizing space resources from the celestial bodies listed above is vital to supporting safe and sustainable space exploration. They also commit to informing the U.N. Secretary General, the public and the scientific community of space resource extraction activities.

Deconfliction of Activities: The Artemis Accords nations are committed to preventing harmful interference and exercising the principle of due regard. This also covers the establishment of so-called "safety zones" with areas that can be established between countries and which can be ended when relevant operations cease.

Orbital Debris: Artemis Accords countries are committed to planning for the safe timely and efficient disposal of debris as part of the mission planning process. Signatories of the accords also agree that they should limit the generation of new long-lived or harmful debris. This includes the safe disposal of space structures in the post-operation phase of missions.

Conflict of Interests

The authors have no conflict of interest to declare related to this article.

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