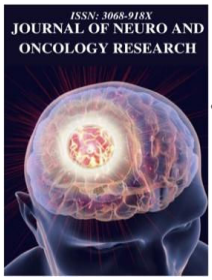

ISSN: 3068-918X
Journal of Neuro and Oncology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Letter To Editor

Neuroscience Research Priorities for Space Settlement: Is It Time to Focus on Brain Derived Neurotrophic Factor (BDNF)?

Margaret Boone Rappaport[1*], Christopher J Corbally[2]

[1]The Human Sentience Project, Tucson, AZ, USA

[2]Vatican Observatory, University of Arizona, Tucson, AZ, USA

***Correspondence author:** Margaret Boone Rappaport, The Human Sentience Project, Tucson, AZ, USA; Email: msbrappaport@aol.com

Citation: Rappaport MB, et al. Neuroscience Research Priorities for Space Settlement: Is It Time to Focus on Brain Derived Neurotrophic Factor (BDNF)? J Neuro Onco Res. 2025;5(3):1-4.

https://doi.org/10.46889/JNOR.2025.5305

Received Date: 14-10-2025

Accepted Date: 27-10-2025

Published Date: 04-11-2025

Stellar Findings without Follow-Up Yet

The stellar research findings from work by Popova, Naumenko and Colleagues 10-15 years ago was arguably the discovery that Brain Derived Neurotrophic Factor (BDNF) may well be stable in spaceflight in the rodent model. At the same time, other neurotrophic factors (CDNF and GDNF), neurotransmitters 5-HT (serotonin risk-and-reward system) and DA (dopamine risk-and-reward system) were found to be not stable in mice at around a month in space [1-4].

These researchers also identified parts of the brain that were particularly sensitive to spaceflight, as well as "risk neurogenes", which affect both serotonin and dopamine pathways [3]. Their painstaking work down to hormonal and genetic levels begins to scratch away at the shroud that makes all of us appreciative of just how complex human affect, cognition and decision-making are and how they might change when humans venture off planet Earth-further increasing the complexities.

As an important factor in humans' high level of neuroplasticity, BDNF plays a significant role in learning, memory and general cognitive functioning. BDNF has been helpful on Earth in a variety of therapies, which suggest ways for it to be used in space settlement. Either in spaceflight or in settlements in less than full gravity, with cosmic radiation that forces humans to be confined in vehicles or habitations with high levels of CO_2, BDNF's application well might prove salutary.

Importance for Human Settlement Off-Earth

While cautions are appropriate for research that has not yet been replicated for humans in space, including flight lengths necessary for settlement, the logical extrapolation is that BDNF could have some stability in humans during spaceflight. There may be something different and important about the way BDNF operates in mammals during spaceflight. This would not be the first time that research on lower mammals pointed to potentially fruitful inquiries for humans and if those inquiries lead to the same or similar results, then, to program options for humans that are extremely important in off-Earth settlement.

Our conclusion is that these early findings in the rodent model should be replicated in humans as soon as possible so that researchers and space program planners can begin as soon as possible to conquer the "challenges in translational neuroscience", as noted recently by editorial board members of Exploration of Neuroscience [5]. The potential is too important given the jumble of symptoms and difficulties that human spacefarers have had to date from problems with inner ears, balance, mood, anxiety, depression and cognitive decline [6]. Indeed, BDNF has been used for some of these problems on Earth.

The Neuroplastic Species and Its Space Technology: Why Are Sequelae Not Worse?

It is important to note that, as of this writing, around 676 humans have gone to space and most returned without long-term disabling conditions; 21 have died in training, launch or in space. We conclude this is a fairly good and hopeful record. It suggests that something is operating biologically to allow humans to adapt to space to at least a certain degree and at least temporarily. In our review and analysis of neuroplasticity in spaceflight, we return repeatedly to the seemingly circular explanation as to why the human species does not fare worse in space [7]. The answer always came back: Humans are the most neuroplastic species alive. Their neurological systems are, if not "well adapted to spaceflight", at least tolerant of it to a point that reasonable remediations in diet, exercise and some medications will allow them to fulfill missions successfully. This sounds like a facile conclusion, but surely it is not. Humankind's success in space ventures to date has, in our view, been quite remarkable given the variety of deconditioning symptoms that we tentatively named "Spaceflight Neuroplastic Syndrome" [8].

Support for Off-World Medical Research Shifts toward Commercial Companies

Since the time that data on the rodent model were collected from several existing space stations and analyzed by Popova and Colleagues, there have been social and economic changes that have challenged the collection of parallel data on humans in spaceflight. Still other changes have shifted focus from nation-state space programs to a greater emphasis on commercial space programs. University and hospital-based neurology colleagues should keep in mind that commercial space programs (many of which are still small) do not have longstanding and administratively supportive infrastructures for scientific experiments and analysis of data using the best computer programming. However, commercial space programs are now positioned to begin to collect data on humans in space or they soon will be. It appears that there may be an emerging mismatch between a focus on space research and traditional research funding and supportive infrastructures. It is important that small commercial space companies have access to the best available computer analysts. In addition, many small space start-ups are not prepared for this type of bio-medical research unless they are convinced their investment may "pay off" in the long run.

In our literature review for this commentary, we encountered the beginning of what will surely be a flood of reports on using Artificial Intelligence (AI) large language models to understand molecular pathways, structures and the fitting of molecular components. Zhu and Colleagues write, "We developed an Artificial Intelligence (AI) model to predict the three-dimensional protein structures of BDNF and TrkB, as well as their interaction. The AI model was further applied to compare small-molecule drugs that mimic BDNF-TrkB interaction" [9]. This takes "bench neuroscience" to a new level and off the planet, if possible. We view the transition from nation-state to commercial dominance in space programming as a natural and planned development, in which private space endeavors were always meant to overtake dominance from NASA in research. We view NASA's future as an important regulatory agency, much like the European Space Agency and its important work in space debris removal [10,11]. Given the variety of public and private enterprises that will be using cislunar space, there is a great need for a strong regulatory framework that can monitor compliance with the best of the Artemis Accords, now managed by the US State Department [12]. In sum, our view is that the transition to the dominance of commercial space programs was inevitable and will be fruitful. However, the follow-up research needed to investigate neurotransmitters and neurotrophic factors in humans, during spaceflight, has apparently been left behind in these times of transition.

Established Research Programs Need New Partners in Commercial Space Start-Ups

In this environment, space research needs to continue to fully involve university and medical programs that have research facilities, equipment and computer know-how. However, most universities do not have space vehicles ready and waiting for research in orbit yet. Therefore, small space start-up companies will be required for partnerships with more established research institutions. It may seem like a "step down" for universities, but we are convinced it is truly a "step up", i.e., a mechanism to join the enormous medical research enterprise that will focus on humans in space. These changes are sure to come because they are well needed. Whether they are medically prepared or not, humans will go to space soon, in large numbers and some will settle on the Moon and Mars. With important decades devoted to the space settlement of humans there and ultimately in the Asteroids and orbiting around moons of the gas giants, Jupiter and Saturn, there is a pressing need to understand the lead that research on BDNF in spaceflight has uncovered in the rodent model. Can BDNF, as a natural component, be used to augment human neurological systems and not just the brain, because ocular and auditory functioning has been found to be impaired among some humans in space. The limbs, too, are less efficient when one first returns to full gravity. It is the neurology of the entire human being that will be of concern, while more and more people leave Earth, travel elsewhere and return in space vehicles (some of which are on the drawing boards now).

On Earth, BDNF has been used to counter "space fog" (confusion, lapses in short term memory) "sensory reweighting", that could be important for space explorers who have to adapt to different gravities (like the Moon's 1/6 gravity or Mars' 1/3 gravity); and stress because of loss of sleep, isolation and confinement in spaceflight, which are all known to impact cognitive functioning. In particular, it has been suggested that BDNF can help depression and anxiety and mood regulation, in general [13]. The human body carefully regulates BDNF in response to genetic and environmental factors. The better this complex regulation is understood, the more helpful BDNF can be in off-world circumstances. However, it would surely have to be carefully monitored at first.

Issues in Delivery of BDNF to Neurological Tissues

There are issues involved in the delivery of BDNF, especially overcoming difficulties in bridging the Blood-Brain Barrier (BBB), which should be solved before use off-Earth. Yet, there is active research in this area. Ongoing efforts include the following mechanisms: intranasal delivery, nanoparticle-mediated delivery, gene therapy, viral vectors to deliver the BDNF, cell-based delivery especially bone marrow stem cells, focused ultrasound enhanced intranasal delivery (FUSIN disrupts the BBB and enhanced delivery efficiency by targeting delivery to specific brain regions perhaps those that Popova and colleagues first identified in 2020) and finally, BBB modulators, peptides like ADTC5 that can transiently modulate the BBB, allowing BDNF to cross and reach brain regions [14-16]. To summarize, BDNF has been used on Earth as a treatment for stress resilience, to improve cognitive function, for depression and fatigue and for neuro-protection from inflammation that may be greater in, for example, a lunar environment. There are good and varied efforts to solve the issues of delivery of BDNF to brain tissues.

When Is It Reasonable to Transfer Treatment Types Off-Earth?

A reasonable question arises as to whether this variety of therapeutic approaches makes sense in a new environment with low gravity and higher cosmic radiation. We understand BDNF's effects on Earth. What we do not know is how well those results extrapolate to the Moon or Mars. Either lunar or martian gravity may be enough to forestall some of the de-conditioning problems encountered in the microgravity of space. If this is true, all the better. If it is not true, then all the more apparent need for treatments like BDNF.

We say this cautiously, without full knowledge of BDNF's mechanism of action. Is this wise? Is this potentially dangerous? These are good and rightful questions that potential space travelers need to be asking of themselves and their sponsors and still, humans are going to be off planet Earth soon and there is perhaps not the correct set of circumstances to do the testing that would usually be necessary. Our perspective is to have BDNF available. We ask: Did early humans worry about the effects of willow tree bark on their stomach linings? Probably not. Perhaps they were more focused on getting rid of a headache or a fever. Did they know how aspirin worked? No, it was not necessary and through trial and error they came to see aspirin as relatively benign. The conundrum is similar to the one today regarding all types of medications off-Earth..

BDNF As an Early Proxy Measure for Neuroplasticity

We have suggested that BDNF could be an early proxy measure for neuroplasticity, itself. If it is used that way, then we may come to a deeper understanding of this amazing capacity that humans have, apparently, more than any other terrestrial creatures. Using BDNF as a proxy measure would enable many forms of research that are now "hanging fire" because neuroplasticity is not fully understood. In Popova, Naumenko's and Colleagues' remarkable work we come closest to understanding neuroplasticity at some of its genetic and hormonal roots.

Conflict of Interest

The investigators declare no material or financial conflict of interest related to this study.

Funding Sources

None.

References

1. Popova NK, Ilchibaeva TV, Naumenko VS. Neurotrophic factors (BDNF and GDNF) and the serotonergic system of the brain. Biochemistry (Mosc). 2017;82(3):308-17.
2. Popova NK, Kulikov AV, Kondaurova EM. Risk neurogenes for long-term spaceflight: Dopamine and serotonin brain

system. Mol Neurobiol. 2015;51(3):1443-51.
3. Popova NK, Kulikov AV, Naumenko VS. Spaceflight and brain plasticity: Spaceflight effects on regional expression of neurotransmitter systems and neurotrophic factor-encoding genes. Neurosci Biobehav Rev. 2020;119:396-405.
4. Naumenko VS, Kulikov AV, Kondaurova EM. Effect of actual long-term spaceflight on BDNF, TrkB, p75, BAX and BCL-XL gene expression in mouse brain regions. Neuroscience. 2015;284:730-6.
5. Hermann DM, Bacigaluppi M, Bassetti CL. Most prominent challenges in translational neuroscience and strategic solutions to bridge the gaps: Perspectives from an editorial board interrogation. Explor Neurosci. 2025;4:1006106.
6. Yin Y, Liu J, Fan Q, et al. Long-term spaceflight composite stress induces depression and cognitive impairment in astronauts insights from neuroplasticity. Transl Psychiatry. 2023;13(1):1-7.
7. Rappaport MB, Corbally CJ. Neuroplasticity as a foundation for decision-making in space. NeuroSci. 2022;3(3):457-75.
8. Rappaport MB, Corbally CJ. Toward an etiology of spaceflight neuroplastic syndrome: Evolutionary science leads to new hypotheses and program priorities. NeuroSci. 2023;4(4):247-62.
9. Zhu J, Zou J, Li F. Evaluation of neuroprotective agents acting via the BDNF-TrkB pathway using AI-enabled predictions of ligand-receptor interactions. MedComm Future Med. 2022;1(1):e15.
10. Anonymous. ESA space environment report 2025. [Last accessed on: October 27, 2025] https://www.esa.int/Space_Safety/Space_Debris/ESA_Space_Environment_Report_2025
11. Rappaport MB, Corbally CJ. Options for regulating satellite and other space debris in cislunar space. Int J Aerosp Sci Commun. 2025;1(5):1-3.
12. U.S. Department of State. Artemis accords. 2025. [Last accessed on: October 27, 2025] https://www.state.gov/bureau-of-oceans-and-international-environmental-and-scientific-affairs/artemis-accords/
13. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: A key molecule for memory in the healthy and the pathological brain. Front Cell Neurosci. 2019;13:363.
14. Pardridge WM, Kang YS, Buciak JL. Transport of human recombinant Brain-Derived Neurotrophic Factor (BDNF) through the rat blood-brain barrier *in-vivo* using vector-mediated peptide drug delivery. Pharm Res. 1994;11(5):738-46.
15. D'Souza A, Dave KM, Stetler RA. Targeting the blood-brain barrier for the delivery of stroke therapies. Adv Drug Deliv Rev. 2021;171:332-51.
16. Vitaliano GD, Kim JK, Kaufman MJ. Clathrin nanoparticles deliver BDNF to hippocampus and enhance neurogenesis, synaptogenesis and cognition in an HIV/neuroAIDS mouse model. Commun Biol. 2022;5(1):236.