Cerebrum, April 2021

Space Between the Ears

By Mark Shelhamer, Sc.D.

What can spaceflight teach us about the brain? Our author, Mark Shelhamer, former chief scientist for the NASA Human Research Program and a professor at the Johns Hopkins School of Medicine, lays out how spaceflight relates to brain function, cognitive performance, and mental abilities.

A few short months ago, news programs around the globe showed NASA engineers and scientists celebrating as a robot named Perseverance successfully landed on the surface of Mars. The mission: capture and share images and audio that have never been seen or heard before. As impressed as most observers were of this major milestone, many couldn't help but wonder when we might be ready to someday send humans. While it seems the stuff of science fiction and almost inconceivable, the answer—according to recent NASA planning—is before the end of the 2030s, less than two decades away.

There are still many obstacles to accomplishing such a feat, many of which have to do with overcoming cognitive and mental health challenges that would impact a crew: long-term isolation, eyesight impairment, and psychological effects from the stress of danger and what could amount to life-or-death decisions. For a mission to succeed, high mental and cognitive function would be absolutely critical; astronauts would be called on to perform demanding tasks in a demanding environment. Losing 20 IQ points halfway to Mars is not an option.

Finding the answers to overcoming those obstacles has not only offered us the opportunity to advance spaceflight, it also allows us to apply what we learn to help people here on Earth. While we haven't yet seen anything as a dramatic as a clear loss of intellectual capacity in space, there are enough indicators to suggest that we should pay close attention.

Stress—an emotional or mental state resulting from tense or overwhelming circumstances—and the body's response to it, which involves multiple systems, from metabolism to muscles to memory—may be the chief challenge that astronauts face. Spaceflight is full of stressors, many of which can have an impact on brain function, cognitive performance, and mental capacities. Several changes in brain structure and function have been observed [in astronauts after spaceflight]. The full implications of these changes for health and performance are not yet known, but any adverse consequences will be increasingly important as spaceflights become longer and more ambitious (such as a three-year mission to Mars).

Name something stressful in your day-to-day routine, and it is likely also present in spaceflight—along with stressors that are unique to the context. *Failure is Not an Option*, the title of NASA Flight Director Gene Kranz's memoir in 2000, convincingly sums up the situation. High workload is a common feature of spaceflight. Space programs (national or commercial) do not incur the expense of sending people into space for them to rest and relax. On the contrary, astronauts' daily schedules (at least in the US program) are planned in great detail, and their progress in keeping on schedule is tracked in real time. And there is much to be done during a mission, from normal spacecraft operations, maintenance, and repairs, to a wide range of science experiments and assessments of new space technology. Much of the science, in fact, is dedicated to understanding the human response and adaptation to spaceflight.

Along with the high workload, sleep disruptions and misalignment of circadian rhythms are not uncommon. The normal light-dark cycle, which ordinarily provides a temporal structure to the day and entrains biological rhythms, is missing. Alarms of various kinds repeatedly awaken astronauts to conduct necessary tasks, and the pervasive sense of danger, lest something go wrong, can also be disruptive. All of these contribute to fatigue and stress.

Such factors may not be unique to spaceflight, but the level of isolation and confinement astronauts experience is certainly unlikely to be found at home. As far as spacecraft go, the International Space Station (ISS) is large, but it is still small compared to the indoor and outdoor spaces we have access to here on Earth. There is no such thing as "going out for a walk," without a great deal of preparation, special and cumbersome suits, and attendant increased risk. Add to this the fact that, while the view outside may be spectacular, astronauts aren't tasked to look out the window but rather to work inside, where they see the same people and the same scenery day after day, month after month. The stress of interpersonal relations under such circumstances can be challenging.

Then there are factors that are even more specific to space travel. The level of carbon dioxide in a spacecraft is typically much higher than here on Earth, because it is expensive in terms of supplies and energy to reduce it. Elevated CO_2 produces such effects as irritability and headache—not the types of things that are conducive to working with others in a small space. The radiation level is also elevated—although not as high as it is on the moon or Mars, or in deep space on the journey there. The primary long-term risk from radiation is an increased lifetime likelihood of cancer, but there are possible short-term effects as well. There is some evidence from animal studies that a large acute radiation dose (as might result from a solar flare) could cause a deficit in cognitive function. While this remains to be verified in humans, the prospect of a drop in mental capacity when it is most needed—for example, in mid-journey to Mars—should give one pause.

Finally, there is weightlessness itself. It is perhaps odd to think of this as a stressor, when we see astronauts cavorting in zero gravity, free to explore the full three-dimensional scope of their confines. But this freedom comes with challenges. Objects, including people, float away if not held in place. Debris floats and can get into the eyes. There are also physiological consequences of the shift of body fluids to the head, which might lead to changes in cognitive function, and certainly contribute to sinus congestion and alterations in the senses of taste and smell.

Astronauts are asked to perform at a very high level in a very demanding situation, under constant supervision and scrutiny; this doesn't help with the stress level. Beyond such external factors, the high standards they set for themselves may lead to self-imposed stress. A mission is often the peak of one's professional career, a position of high visibility in which errors of judgement can have immediate and dire consequences. Astronauts are well-prepared and highly trained to overcome and cope with stressors that would be unbearable for most of us. Nevertheless, they are human. Stress takes a toll, especially over the long run and when down-time for rest and recovery is hard to come by. While we understand a great deal about these stressors individually (even if we do not yet know how to counter them effectively), their combination, over an extended period, could lead to problems that we do not yet foresee. In this regard, human spaceflight is not only an exploration of space itself, but also of human limits and capabilities.

Effects of Stress

What are the effects of these myriad stressors on brain function and mental performance? We know some, and others might become apparent on more ambitious missions such as a trip to

Mars. A common observation among astronauts refers to a phenomenon known as “space fog” or “space stupids”—a sense of cognitive slowing and the need for increased mental effort to perform routine tasks.

Disrupted sleep and elevated CO_2 alone, in a demanding setting under intense pressure to perform, could easily produce such cognitive problems. Add all the other spaceflight stressors described above, and it is not hard to imagine having even greater difficulty concentrating and a sense of mental lethargy. Related to this is the phenomenon of “neurasthenia”: a vaguely defined sense of fatigue, lack of motivation, irritability, and related somatic sensations.

Strangely, though, objective testing of cognitive function in space does not fully support these subjective observations. In-flight cognitive testing shows variable effects and is hampered by a small number of astronaut subjects and poorly controlled conditions (differences in flight experience, fatigue level, sleep, etc.). A laboratory experiment provides a much better-controlled setting, but it cannot reproduce the reality of space travel that we desire to capture.

In fact, what space data we do have show few, if any, significant decrements in objective measures of cognitive function. There are some changes in reaction time, for example, but their significance is uncertain. This is similar to the case in which a terrestrial patient has a complaint but testing yields no anomalous results in the clinic. Is the test inappropriate, or are the self-assessments incorrect? Or, as is more likely, is it the fact that motivated high-performing individuals can rise to the occasion and perform well on virtually any well-defined task, as long as other distractors can be ignored? In the real world (and especially in space), people rarely have this luxury, which suggests why cognitive testing fails to capture the effects of spaceflight stressors in a realistic way.

What Happens to the Brain?

One such effect relates to changes in visual function. Astronauts returning from early missions of several months on ISS sometimes reported changes in visual acuity. Given all the demands of spaceflight, and the fact that these astronauts aged several months during their missions at a time in life when normal aging often produces decrements in visual function, it was hard to know what to make of these reports. Eventually, it became clear that there were changes in the structure of the eye—mostly temporary but some apparently long-lasting—that were very troubling. Alterations in visual function in high-performing individuals in a dangerous and demanding environment is something that gets a lot of attention, and a great deal of research has been devoted to characterizing and addressing this concern.

What is the cause? It has been recognized for decades that, in weightlessness, there is a shift of fluids (i.e., blood, cerebrospinal fluid, lymph) from the lower to the upper body. This results in puffy faces (easily seen in astronaut photographs), sinus congestion, and blunted sensations of taste and smell. There are also changes in fluid drainage from the head, resulting in a buildup of fluid and presumably an (as yet unproven) increase in intracranial pressure. Some of the fluid makes its way down the sheath—the outer covering—of the optic nerve that leads to the eye. Among other things, this flow of fluid slightly distorts the shape of the eyeball, which changes its optical properties and hence visual acuity.

There are also indications of damage to the retina, the layer of nerve cells in the eye that senses light and sends signals to the brain and that can detach from the epithelium. In advanced degeneration, the macula may bleed and leak fluid. Yellow deposits appear and vision becomes blurry. So far, these ocular effects have not produced dramatic deficits in astronauts' ability to perform their duties, but they are worrisome. They began to generate serious concern when they became more consistent in ISS crews who spent several months in space (as opposed to crews of Space Shuttle missions who spent a maximum of 17 days there). Particularly disturbing is the possibility that these eye changes are but the canary in the coal mine: an indication of broader and more substantial neural damage that might result from longer flights. (A Mars mission would be about three years, albeit with a long period of Martian gravity which might halt the progression of such weightlessness-induced problems.)

In fact, a number of recent imaging studies have examined the brains of astronauts before and after spaceflight. In some cases, these studies show a slight upward shift of the brain in the skull, and an increase in the size of the ventricles (fluid-filled spaces inside the brain where cerebrospinal fluid is made and stored). Not all of these changes are reversed after return to

Earth. There are also changes in neural gray matter, which increases or decreases depending on the functions carried out by the brain area involved, and alterations in connectivity between regions, indicating neural plasticity and reorganization.

Researchers have also observed white matter changes in several areas of the brain, including the cerebellum, which is involved in motor control and vestibular processing. So far, it seems that no permanent or dramatic damage to the neural tissue of the brain has resulted from spaceflight. In fact, many of the changes seen in imaging studies may be appropriately compensatory and adaptive for weightlessness—they are the body's natural adaptive response to an unusual environment and serve the person well as long as he or she is in space. However, even the small possibility of long-lasting neural damage due to brain shifting or increased fluid volume—along with a possibly dire impact on in-flight performance—calls for careful study and monitoring.

Underlying Brain Function Issues

There are other physiological changes that occur during spaceflight that might impact brain function, whose effects are likely to be subtle compared to those above, but could combine synergistically with stressors in ways that we do not yet understand. One example involves the gut microbiome: the millions of microorganisms that live in the intestinal tract.

Among its varied functions, the microbiome appears to influence cognition and emotion through the so-called gut-brain axis; it turns out that maintaining a healthy, vibrant, diversified array of intestinal microbes is important for mental health. For reasons not fully understood, some aspects of this gut microbiome change during spaceflight—possibly the result of the stressors already discussed, along with an altered diet and use of medications for sleep, pain, and other purposes. It seems that bone health, as well, has an impact on brain health through the hormone osteocalcin. Due to unloading of gravity in weightlessness, the bones lose calcium. At least a part of this process seems associated with a reduction in the activity of osteoblasts, which are the cells that create new bone and also secrete osteocalcin.

The vestibular system—the non-auditory part of the inner ear that regulates balance—also plays a crucial role in spaceflight. The brain depends on the presence of gravity as transduced by the vestibular system—a constant throughout evolution and development—to provide a reference frame for spatial orientation. In space, the lack of normal gravitational influence on this system can result in space motion sickness, disorientation, and a variety of related effects. The resultant difficulty in spatial perception and navigation could be a contributor to space fog. In fact, more and more evidence relates vestibular dysfunction to cognitive issues. Although the astronaut's vestibular system remains intact, alterations in its function due to changes in gravity level could have subtle but cumulative cognitive effects.

Finally, sleep is critical for the consolidation of memories and for learning. This includes motor learning: the acquisition of skills that require physical manipulation and dexterity, as might be essential in teleoperation of remote manipulators on Mars or the moon. Impaired sleep, which as we've noted is common in space, could undermine the ability to learn such tasks. This is especially important because a mission that takes a long travel time might demand the performance of tasks learned during training, well before the flight began, allowing plenty of time to forget. In-flight training could provide a vital refresher for those tasks, and it would be best if this relearning were not impaired by the inability to consolidate learning during sleep.

Resilience

The body has compensatory mechanisms for many adverse effects of spaceflight, and they work well. But at some point, they reach their limits. Even short of that limit, at what point does the confluence of these effects reduce and erode performance margins and resilience: the ability to recover from an unexpected perturbation or anomaly? This is a perilous problem that is difficult to address.

Astronauts don't get to be astronauts without a full complement of compensatory strategies that they can call upon (volitionally or subconsciously) to work around deficits that occur. They might simply increase their level of concentration, or give themselves extra time, or seek help from a crewmate, or defer some harder tasks until they are better rested. If the brain remains able to carry out this type of logistical re-organizational process, can we say there is actually a deficit? Yet, when faced with an additional stressor such as an emergency alarm, the sudden increase in mental demand might make a latent mental or cognitive deficit manifest—at exactly the wrong time. We do not yet have standardized tests for adaptability and the ability to reorganize in the face of a decrease in brain function.

A similar effect is seen on Earth among some patients with balance disorders. They may present to the clinician performing normally on a specific test of balance, but fail when an additional demand is added. An example is walking in a straight line, and then walking that same line while turning one's head back and forth or responding to random disturbances. The additional task draws cognitive resources away from attention to walking, and automatic walking functions suffer as a result.

The Path Ahead

Why should we care about these observations, since their effects on cognitive performance and mental health can be subtle and vary between individuals? So far, these effects have not caused a US space mission to be canceled or postponed for medical reasons.

But there is one overwhelming reason to care. Future missions will be of unprecedented difficulty and, most notably, require a tremendous amount of crew autonomy. For a future mission to Mars, for example, support from Earth-based experts will be extremely limited, and augmentation of supplies through cargo delivery essentially impossible. One-way radio transmission time can take 20 minutes; obviously that is an enormous time span if an urgent problem needs attention from Earth.

Furthermore, almost by definition, when venturing into an unknown realm, not all of the risks can be identified and mitigated ahead of time. Astronauts on these voyages will need every possible edge to maintain the ability to carry out the mission and return safely. Part of this edge comes from understanding and mitigating the more critical of the concerns discussed here.

Research is currently underway to address some of the multiple effects of future spaceflight. But this is a daunting task, given the complexity and density of interaction, interconnection, and permutations. And as we've seen, it is not just intra-brain interactions that are of interest, but also their interplay with such external factors as sleep, workload, radiation, and other people.

Another question is whether any of what we have learned so far is relevant to earthbound mortals. One might make the case that what happens to highly select individuals, placed under extreme pressure in an unusual environment, has little to do with the rest of us. Astronauts are certainly not average people, as far as test subjects go. Selection requires that they are healthy, fit, and maintain healthy lifestyles. They need to be extremely compliant and follow directions; we are able to continuously monitor and measure nutrition, exercise, sleep, workloads, and task challenges.

But the overall research opportunity provided by space travel will allow us to understand how the brain adapts to multiple stressors, presented simultaneously, over long periods of time. Studying astronauts (especially while in space) dramatically reduces uncontrolled factors, which are troubling confounds in terrestrial studies. Spaceflight stressors and other challenges are indeed different and may never be matched with those on Earth. The manner in which the brain reorganizes to compensate for them, however, can tell us a great deal that is relevant to our own compensatory capacities in the face of disease and aging.

Bio

Mark Shelhamer, Sc.D., is professor in the Department of Otolaryngology—Head & Neck Surgery at the Johns Hopkins School of Medicine, where he started as a postdoctoral fellow in 1990. He has bachelor's and master's degrees in electrical engineering from Drexel University, and a doctoral degree in biomedical engineering from MIT. At MIT, he worked on sensorimotor physiology and modeling, including the study of astronaut adaptation to space flight. He then moved to Johns Hopkins where he continued the study of sensorimotor adaptation with an emphasis on the vestibular and oculomotor systems and nonlinear dynamics. From 2013 to 2016 he served as chief scientist for the NASA Human Research Program. His research since that time has emphasized multi-system and cross-disciplinary interactions that contribute to personal and mission resilience in spaceflight.