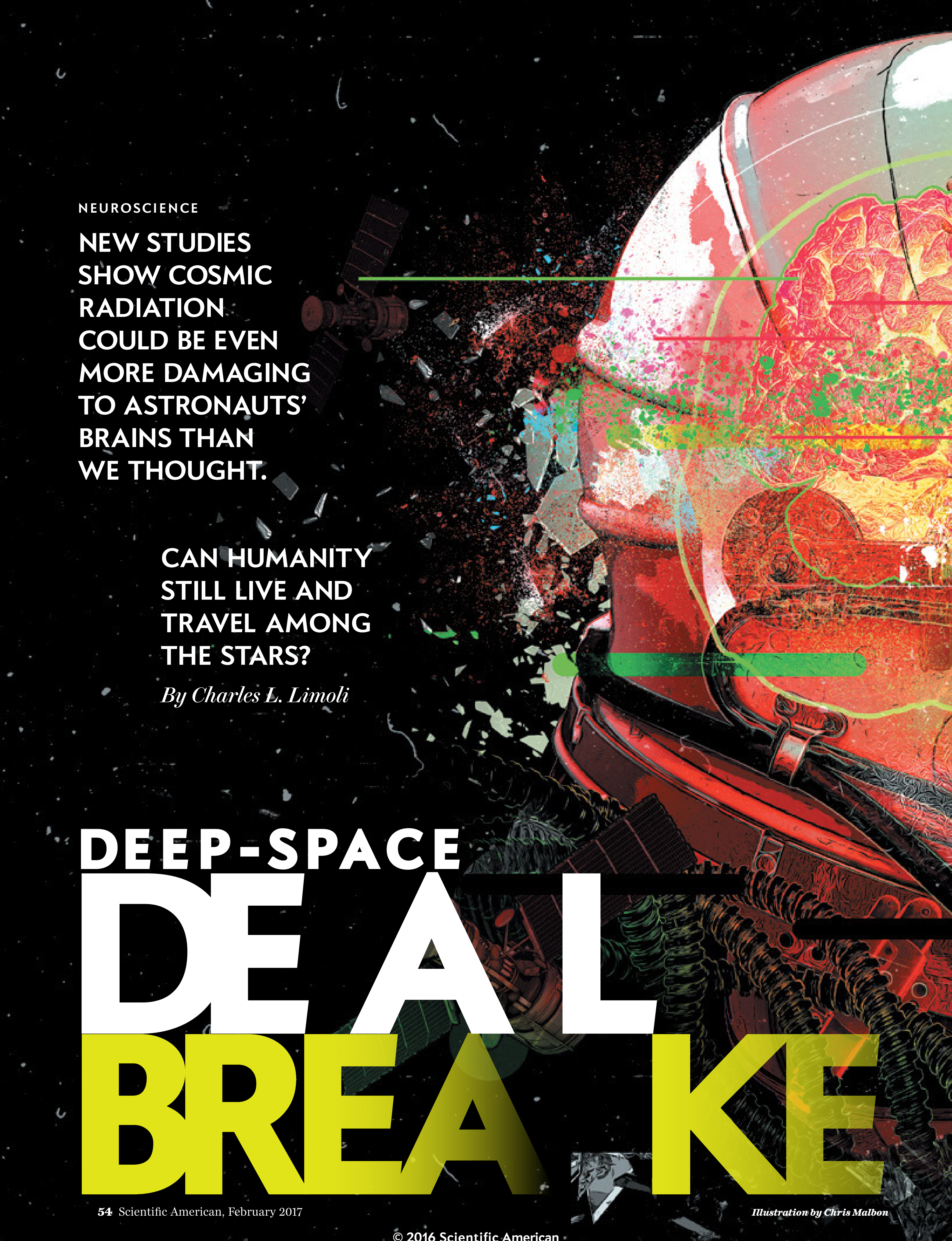

NEUROSCIENCE

NEW STUDIES SHOW COSMIC RADIATION COULD BE EVEN MORE DAMAGING TO ASTRONAUTS' BRAINS THAN WE THOUGHT.

CAN HUMANITY STILL LIVE AND TRAVEL AMONG THE STARS?

By Charles L. Limoli

DEEP-SPACE
DEAL
BREAKE

Illustration by Chris Malbon

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FOR MILLENNIA HUMANS HAVE GAZED INTO THE NIGHT SKY AND DREAMED OF TRAVELING to the stars. Now that people have walked on the moon and lived in orbit on the space station, it seems inevitable that we will venture farther, to Mars, the rest of the solar system and beyond. The dream is common to many cultures and occupies the space agencies of nations around the world.

Yet we know that space is dangerous. Every time astronauts leave Earth, they face extreme cold, the lack of an atmosphere, microgravity and radiation exposure. These hazards have seemed mostly surmountable so far—mere engineering problems to be figured out and risks that brave space travelers willingly take on. Yet new research, by myself and others, has shown that the radiation in space may be more damaging than we thought, particularly to the fragile yet vital human brain. Although scientists have known about the radioactive nature of space for decades, only recently has evidence emerged of how serious the effects of radiation are on the brain and how long they last.

By irradiating mice, my colleagues and I have measured significant and enduring cognitive impairment that is likely to translate to humans as well, potentially endangering the success of space missions. Although astronauts on the relatively low-flying International Space Station are largely shielded from the worst effects by their perch within the edges of Earth's atmosphere, they run the risk of some cognitive damage. The dangers for voyagers to Mars and beyond, however, could be grave.

We currently have a limited ability to mitigate these perils. Improved shielding for spacecraft could block some radiation, but no known material is lightweight enough to be practical. Drugs that could fight the effects of radiation inside the body are only in the early stages. Unless we find a successful solution, humanity's dreams of journeying throughout the solar system and beyond may be forever out of reach.

POWERFUL PARTICLES

COSMIC RADIATION is pernicious—we cannot see or feel it, yet it fills every inch of what looks like empty space and can do significant damage to human tissue. Most dangerous to astronauts are galactic cosmic rays (GCRs), charged atomic nuclei flying at nearly the speed of light that astronomers think originated in the supernova remnants of dead stars. In addition to GCRs, which pervade the cosmos as a uniform field, our sun also ejects protons (ionized hydrogen) of multiple energies. Although protons constitute most of the radiation in space, because of their lighter mass they cause considerably less damage to our bodies compared with heavier particles. Most important, all these particles possess sufficient energy to traverse the hulls of spacecraft and the bodies of astronauts. Whereas the magnetic fields surrounding planet Earth protect terrestrial inhabitants by deflecting most of these cosmic particles away from the surface, travel beyond the magnetosphere leads to unavoidable exposure and the unfortunate consequences of these particles' interactions with human tissue.

The problem with cosmic radiation is that when these particles pass through the human body, they leave behind some of their own energy that "ionizes" atoms in the tissue—that is, knocks electrons off the atoms, causing them to turn from neutral atoms into charged ions. The charged particles then move along their own trajectories, knocking more electrons loose and generating secondary tracks, causing a widening trail of damage.

IN BRIEF

Space travel has always been dangerous, but new research shows that cosmic radiation is even more harmful to the brain than we knew.

Scientists irradiated mice with charged particles simulating the radiation astronauts get in space and found both behavioral declines and neural damage.

Better shielding for spacecraft and space suits or drugs that protect the brain will be necessary to allow humanity a future among the stars.

The heavier the radiation particle, the more energy it will have and the more atoms it will ionize.

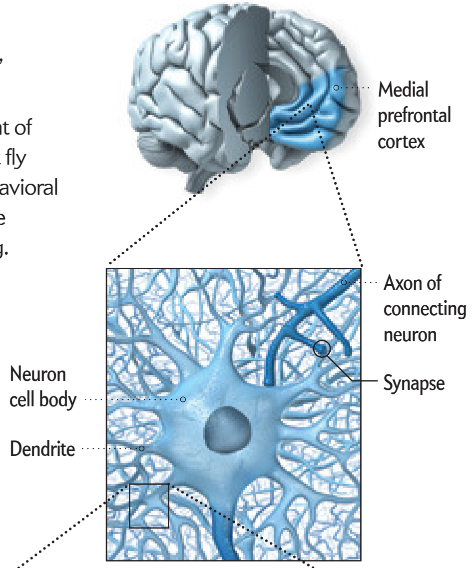
The redistribution of these electrons causes some atoms to break their molecular bonds, damaging proteins, lipids, nucleic acids and other vital molecules in the cells and tissues of the body. This removal of electrons forms free radicals—atoms or molecules that lack the full complement of electrons to fill their atomic orbitals, making them highly reactive and eager to pair with other electrons from adjacent atoms or molecules to fill up their orbitals. The free radicals can then react with other molecules in the body, turning them into new chemicals that do not serve their original purpose. When radicals encounter DNA, for example, they can break apart its sugar phosphate backbone or damage the nucleic acid bases.

Scientists measure radiation exposure in "absorbed doses"—the energy lost by the radiation and deposited in the body (per unit of body mass). The SI unit for absorbed dose is the gray (Gy), where 1 Gy is one joule per kilogram. Radiation also comes in different "qualities," which refers to the density of ionization it produces per unit dose. Scientists characterize radiation types by their linear energy transfer (LET), or the amount of energy lost per distance traveled. For example, a dose of high LET radiation is more dangerous than the same dose of low LET radiation because it leaves behind more energy and thus causes more atoms to ionize. The resultant damage is therefore more difficult for the cell to repair and recover from. Because many of the radiation types encountered in GCRs have a relatively high LET, this characteristic has important implications for deep-space travel, which we will discuss later.

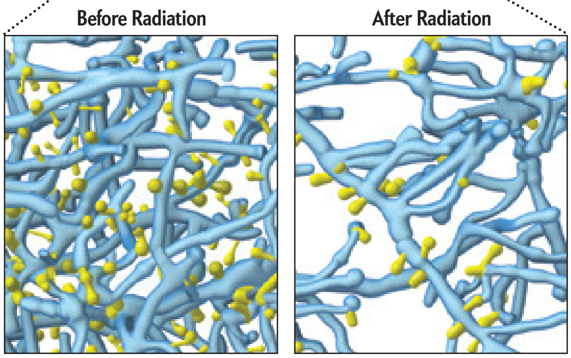
RESEARCH FINDINGS

Space Brain

Cosmic radiation may harm astronauts' brains more than previously thought. Scientists exposed mice to an onslaught of charged particles mimicking those that fly through space and measured both behavioral performance and physical damage. The damage was revealed by brain imaging.



Spacelike radiation damaged a region of the mouse brain called the medial prefrontal cortex, which is associated with memory. In this area, neuron protrusions called dendritic spines decreased in size and number.


Before Radiation
After Radiation

Dendrites receive chemical signals from other neurons. Eight weeks after exposure to 30 centigrays of radiation, the mice showed a 20 to 40 percent reduction in the number of dendritic spines (*yellow*), small branches off the main dendrite shaft that enable learning and memory.

SOURCE: "WHAT HAPPENS TO YOUR BRAIN ON THE WAY TO MARS," BY VIPAN K. PARIHAR ET AL., IN *SCIENCE ADVANCES*, VOL. 1, NO. 4, ARTICLE NO. E1400256; MAY 1, 2015

Energetic heavier radiation particles can leave tracks of higher radical density and increased destruction from ionizations compared with particles of lower mass. At the molecular level, we find nanometer-wide regions of high radical density that can lead to relatively small volumes containing a large number of damaged sites on critical molecules. Thus, heavier charged particles produce much higher yields of these regions of "clustered" damage compared with photon radiation (such as x-rays and gamma rays). It is this density of damage that makes space radiation more dangerous than traditional types of ionizing radiation found on Earth.

RE-CREATING SPACE ON EARTH

DESPITE THE UBIQUITY of charged particles in space, reproducing these types of radiation fields on Earth to study their effects presents considerable challenges. One of the only places in which we can run experiments simulating space radiation is the NASA Space Radiation Laboratory, a facility NASA and Brookhaven National Laboratory commissioned in 2003 on Long Island. There large particle accelerators speed up ions of various masses to velocities approaching those of space radiation. Experimenters, including myself, place targets—in our case, mice—in the path of this radiation and measure its effects. These tests can show us how specific types of cosmic radiation, at various doses, affect living tissue.

Recently we exposed six-month-old mice to low doses (0.05 to 0.30 Gy) of charged particles (oxygen and titanium, for instance) and tested their behavior. The mice completed tasks called novel object recognition (NOR) and object in place (OiP) to evaluate how the radiation affected their memory and thinking. First, the rodents explored an empty box around three feet square. Then we introduced Legos, rubber ducks and other toys to the box and let the mice wander around a bit more. Later—in some trials after just minutes and in others after hours or a day—we switched the objects for new toys (NOR) or changed the location of the toys (OiP). A smart, healthy animal will seek out novelty and spend

Illustration by Emily Cooper

more time exploring the new toy or location than objects that have stayed the same, whereas an impaired mouse will spend less time poking around. Such tests have proven to be reliable indicators of various types of hippocampal (memory and learning) and cortical (thinking) functions. We measure an animal's performance through what is called a discrimination index, calculated as the time spent at the novel object or location divided by the total time spent exploring both new and old situations.

Our experiments with the NOR and OiP tasks showed that irradiation significantly lowers a mouse's discrimination index. After six weeks, the performance of mice exposed to these doses (5 and 30 cGy, or centigrays) had dropped by about 90 percent, changes that were surprisingly consistent regardless of dose. Furthermore, very recent tests indicated that these effects last 12, 24 and even 52 weeks after exposure. The results suggest that exposure to similar levels of cosmic radiation may prove problematic to astronauts engaged in critical decision making, problem solving and other vital mission activities.

> **Scientists are developing drug and dietary countermeasures that could mitigate the worst effects of radiation on the brain. Yet all these efforts are in early stages, and none has the potential to be a cure-all.**

TRIMMING THE NEURAL TREE

My colleagues and I also followed up these behavioral tests by imaging brain sections from the irradiated mice. Energetic charged particles traveling through the brain have the potential to profoundly change neuronal circuitry. We wanted to observe any specific physical damage that might correlate with the behavioral changes we found. To do so, we used mice that had been genetically altered so that their brains contained brightly fluorescent neurons that showed up in high-resolution microscopy. We collected a series of fluorescent images of various depths in specific brain areas that we then merged and stitched together to create a three-dimensional representation of the brain.

Our imaging showed significant changes to parts of neurons called dendrites. These are the fingerlike protrusions from the main cell body that receive chemical signals from other neurons (similar protrusions called axons transmit signals). Past studies from our laboratory have found that sparsely ionizing (low LET) x-ray and gamma-ray radiation caused significant reductions in the length, area and branching of dendrites over 10 and 30 days. Collectively we call these changes a reduction of dendritic complexity, a critical parameter that can be compared with the branches of a tree. And our recent study, which we published in 2015 in *Science Advances,* also found that very low doses of charged particles can elicit significant and persistent losses in dendritic complexity.

Moreover, these changes occurred at a specific region of the brain termed the medial prefrontal cortex, a spot known to be involved in memory, which we suspected might be damaged based on our behavioral testing. This is not to say that other regions of the brain were not damaged or that other neural circuitry was not impaired, but our findings demonstrate the benefits of combining behavioral studies with brain imaging to connect the cognitive decline we see with structural changes to specific areas of the brain.

We built on the initial imaging with further high-resolution analysis to search for evidence of other structural alterations such as dendritic spines—small (less than one micron, or a fraction of the width of a human hair)—protrusions from the main shaft of the dendrite that enable learning and memory. If dendrites are branches on a tree, dendritic spines are like the leaves on the branches. Dendritic spines contain the synaptic machinery that allows dendrites to receive neuronal signals, and they come in different shapes that help in various jobs. Our past work with x-rays and protons and more recent work with charged particles have revealed a marked sensitivity of dendritic spines to irradiation. And we found that dendritic spine density, or the number of spines per unit length, significantly decreased after short periods (10 days) and longer times (six weeks) following a mouse's exposure. These serious and persistent effects attest to the capability of charged particles to elicit structural changes of consequence—changes that compromise neurons' ability to mediate neurotransmission by reducing the number of synaptic connections in the brain.

To further underline that the changes in mice's behavior resulted from the changes we found in their neurons, we plotted individual performance against dendritic spine density in the same animal. Our data revealed that as dendritic spine density decreased, so, too, did cognitive ability. Individual animals exhibiting the poorest performance (that is, reduced curiosity or exploration of novelty) also possessed the lowest dendritic spine densities, suggesting that disruption of cognition was at least in part related to reduced numbers of dendritic spines. These data provide the first evidence linking structural damage to the adverse behavioral outcomes observed in animals exposed to cosmic radiation.

These results help to confirm what NASA has suspected for years: radiation may be harmful to astronauts' cognitive performance. Until now, these fears had been based in large part on the clinical literature documenting a range of cognitive effects in patients surviving cranial radiotherapy for treatment of brain cancer. Yet in the past scientists have been hesitant to extrapolate these outcomes to astronauts in space because these are

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different populations being exposed to different types of radiation at different doses. In the clinic, a typical daily dose (2 Gy) would exceed most estimates of the radiation dose incurred during a round-trip to and extended stay on Mars. Interplanetary dose rates are about 0.48 mGy, or milligrays, a day during the roughly 360-day round-trip transit and half that rate during an expected stay of one year or more on Mars (because the planet's bulk blocks the radiation coming from below). Although the total radiation doses used in the clinic are much higher than those found in space, the x-rays and gamma rays typically used to treat tumors are sparsely ionizing (low LET), whereas the charged particles we worry about in space are densely ionizing (high LET). For this reason, we have not been able to make strong comparisons between the outcomes in cancer patients and those we expect in astronauts.

Our work adds new support to the notion that space radiation is harmful to astronauts' brains, but important caveats still persist. Although our experiments used doses of radiation similar to what space travelers would experience, we were unable to deliver those doses at the same rate that astronauts would receive. In space, astronauts would receive the radiation over the course of many months to years, underscoring the protracted nature of cosmic radiation exposure. Because we had only limited time at the accelerator facility, we had to deliver the same dose over a matter of minutes. This large difference in rate might raise doubts about our results because one could suppose that cells would have time to repair and recover when the dose was delivered slowly. In fact, the difference in dose rate is not likely to have a strong effect, because the total dose is low (in other words, particles fly through infrequently), the space particles of most concern are high LET radiation (which produces severe cellular damage that is hard to recover from no matter how quickly it is delivered) and, finally, most areas of the brain cannot generate new neurons easily, which further hinders recovery. And although our findings pertain to rodents, not humans, we have no reason to think a human neuron would respond differently in any significant way to cosmic radiation than our mice's neurons did.

OUR FUTURE IN SPACE?

TO SEND HUMANS OUT into the solar system, we face daunting hurdles. Astronauts will need larger, more powerful rockets than those currently available to reach Mars and other bodies in our solar system, and they will need habitats once they arrive and the ability to use resources at their destination to make water and rocket fuel. We must now add to this list of challenges the need to protect space colonists from radiation, which may prove the hardest barrier to overcome.

The first way we might tackle the problem is via shielding that stops the radiation before it can do any damage—placed either on spacecraft and habitats or in space suits or clothing. At the moment, the only way scientists know how to shield against radiation is with extremely heavy and thick materials such as lead. These do the trick, but they are utterly impractical in space because they are so heavy and would require too much rocket fuel to launch. Efforts are now under way to design advanced shielding materials and engineering controls that can enhance a hull's defense on certain regions of a spacecraft. Astronauts could retreat to these more protected areas during times of elevated solar activity and wear helmets and space suits designed to maximize protection from radiation exposure while spacewalking or even sleeping. It would take a radically better protective material than any that currently exist to make a significant improvement, though.

Scientists are also developing drug and dietary countermeasures that astronauts could take on a regular schedule or after acute radiation exposure (following a major solar storm, for example) that could mitigate the worst effects of radiation on the brain. Antioxidant formulations, for example, have shown promise for limiting some of the damage done to mice exposed to spacelike radiation. Researchers have also made progress in designing chemicals that can bolster brain circuitry to help maintain function after damage has occurred. Yet all these efforts are in early stages, and none has the potential to be a cure-all. The best we can hope is to reduce, rather than eliminate, damage. We must also continue to research cosmic radiation's effects on the brain, as well as the entire body, to elucidate more completely the short- and long-term health risks associated with prolonged exposure.

Our discoveries point to a concern about deep-space travel that has perhaps been underappreciated compared with other dangers. The risk of radiation-induced cancer, for instance, is better known but may actually be of lesser importance because of the long time it takes for most radiogenic cancers to develop. We have shown, however, that even small amounts of cosmic radiation cause neuronal damage and cognitive defects in mice and are very likely to do so in humans as well.

The persistence of these radiation-induced changes is another cause of worry. Scientists have seen no sign that damaged dendritic complexity and spine density can repair themselves after cosmic radiation exposure, and whereas it is premature to refer to such changes as permanent, we have no evidence that neurons recover from this type of injury. Therefore, until researchers find specific interventions that can promote and hasten the healing of the irradiated brain tissue, our best options appear limited to protecting our existing neural circuitry.

Cosmic radiation exposure may well represent one of the more significant obstacles to Mars travel and even more so for longer deep-space missions required to explore more distant worlds. Although some may consider these findings controversial, it remains difficult to dismiss these data and their potential implications for the space program. Does this mean we are forever bound to Earth? Perhaps not. These results may simply represent yet another obstacle that humankind must meet and surpass as we prepare to embark on what may prove to be humanity's most daunting challenge and perhaps even its greatest success.

MORE TO EXPLORE

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