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REVIEWS AND COMMENTARY • EDITORIAL

The Long-term Effects of Spaceflight on Human Brain Physiology

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They used to say if man could fly, he'd have wings. But he did fly. He discovered he had to. Do you wish that the first Apollo mission hadn't reached the moon, or that we hadn't gone on to Mars and then to the nearest star? … I must point out that the possibilities, the potential for knowledge and advancement … Risk. Risk is our business. That's what the starship is all about. That's why we're aboard her.

—Captain James Tiberius Kirk, Star Trek

I'd like to die on Mars, just not on impact.

—Elon Musk, Tesla and SpaceX Founder

The Artemis program, an ongoing collaboration between the National Aeronautics and Space Administration (NASA), U.S. commercial spaceflight companies (eg, SpaceX), and international partners (eg, the Canadian and European Space Agencies), set a long-term goal of establishing a sustainable presence on the Moon, thereby laying the foundation for sending humans to Mars. In December 2017, President Trump signed Space Policy Directive 1 authorizing the lunar campaign, and in February 2020 the White House requested a funding increase of 12% to cover Artemis as part of its fiscal year 2021 budget, for a total of $25.2 billion per year (1). Not surprisingly, there is therefore strong interest in expanding our understanding of the long-term effects of space flight on the human brain, especially because trips to the moon are already planned, a human trip to Mars in the next decade is a possibility (which could take 6–8 months each direction [2]), and extended stays in space are already a reality (cosmonaut Valeri Polyakov holds the record at 437 days for a single mission) (3).

In this issue of *Radiology*, Kramer et al studied the brain after long-duration space flight (4). The authors performed serial MRI on 11 of 54 eligible International Space Station astronauts (10 men, one woman; five astronauts had previous exposure to spaceflight; mean mission duration almost 6 months), both preflight and at 1 week, 1 month, 3 months, 6 months, and 1 year after spaceflight. They found that prolonged microgravity exposure caused the following brain changes: *(a)* an approximate 2% expansion of brain and cerebral spinal fluid (CSF) volumes, attributable to both white matter and lateral ventricular measurements, and these remained elevated at 1-year after spaceflight, suggesting permanent alterations; *(b)* a 13% increase in mean CSF intraventricular (aqueductal) flow velocity, suggesting a reduction in intracranial compliance; and *(c)* in roughly half (six of 11 astronauts), depression of the pituitary dome compared with baseline (average midline height decreased from 5.9 to 5.3 mm), suggesting elevated intracranial pressure during spaceflight.

The authors also noted that the changes in lateral ventricular volume and aqueductal CSF flow parameters resembled those associated with normal-pressure (ie, communicating) hydrocephalus.

These findings are consistent with both previous reports and our understanding of the normal determinants of intracranial pressure. A central tenet of human brain physiology is the Monro-Kellie doctrine, or hypothesis, which states that "the sum of volumes of the brain, CSF, and intracranial blood is constant," and that "an increase in one should cause a decrease in one or both of the remaining two" (5). This principle has considerable implications for understanding the intracranial pressure and CSF volume changes accompanying prolonged exposure to microgravity in general and for the pathogenesis of spaceflight-associated neuro-ocular syndrome in particular.

Testing suggests that visual acuity changes occur about 19% of the time after long-duration spaceflights, with varying degrees of optic disc edema, posterior globe flattening, and cotton wool spots. But a 2012 study in *Radiology* reported up to 60% of International Space Station crewmembers may experience at least minimal subjective alterations in acuity, which might persist for years (6). Awareness of spaceflight-associated neuro-ocular syndrome has raised concerns about the physiologic changes caused by prolonged elevation of intracranial pressure in the absence of normal diurnal postural variability due to gravity (7).

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See also the article by Kramer et al in this issue.

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Indeed, a recent study (8) suggested that long-duration International Space Station flights, but not short-duration space shuttle flights, may lead to changes in cognitive and motor test scores and the development of spaceflight-associated neuro-ocular syndrome. These long-duration flights correlate with brain structural changes in both white matter and ventricular volume, like those found in the cohort studied by Kramer et al (4).

Several studies of other cohorts, including both astronauts and cosmonauts, have shown comparable structural changes in white matter and ventricular volumes after prolonged spaceflight (9). The observations in the study by Kramer et al (4) not only confirm those earlier findings but also help explain them by demonstrating the following results: *(a)* persistent brain and ventricular volume expansion out to 1 year, *(b)* increased peak aqueductal CSF flow velocity analogous to that seen with normal-pressure hydrocephalus, and *(c)* depression of the pituitary gland in over half the astronauts studied. These results, especially the development of pituitary gland deformity together with the Monroe-Kellie doctrine, show that the summed expansion of brain and CSF volumes is not offset by decreases in cerebral blood volume. This expansion presumably results in chronically elevated intracranial pressure accompanied by reduced intracranial compliance (and hence increased CSF pulsatility). The analogy to normal-pressure hydrocephalus is intriguing and leads to speculation that glymphatic pathway dysfunction might explain the increased white matter free water volume in postflight astronauts (4).

Limitations of this study relate to the uniqueness of the data set and include the time delay between preflight baseline imaging and launch, reliance on literature-based normative data to help distinguish the effects of spaceflight from those of normal aging, and inaccuracy in the segmentation of compressed dural venous structures affecting the white matter, ventricular, and cerebral blood volume measurements, to name a few. Finally, there are other considerations for the health effects of microgravity on the body as a whole not yet well studied in long-term missions, such as derangements of intravascular and extravascular electrolyte balance impacting the renin-angiotensin-aldosterone system or causing imbalances in the antidiuretic hormone, atrial natriuretic peptide, and sympathetic and parasympathetic activation (10). Further concerns with space travel include but are not limited to vestibular-autonomic adverse effects, exposure to cosmic radiation, and changes in the gut microbiome. Artificial gravity in the form of centrifugal force or acceleration mitigates the effects of microgravity, but questions remain unanswered, such as the benefit of continuous versus intermittent exposure to artificial gravity. Spacesuits with haptic feedback to the astronaut are also in development (10).

In conclusion, long-duration spaceflight may lead to mild depression of the roof of the pituitary fossa, hyperdynamic cerebral spinal fluid flow, and persistent increased white matter and ventricular intracranial volumes. This constellation of findings is presumed to result in increased intracranial pressure and pulsatility, which may help to explain (and develop strategies to avoid) potential long-term effects of microgravity such as spaceflight-associated neuro-ocular syndrome. Future studies are certain to further enlighten us as we continue to explore and "boldly go" into the next frontier.

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