ORIGINAL ARTICLE

Effects of Spaceflight on Astronaut Brain Structure as Indicated on MRI

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ABSTRACT

BACKGROUND

There is limited information regarding the effects of spaceflight on the anatomical configuration of the brain and on cerebrospinal fluid (CSF) spaces.

METHODS

We used magnetic resonance imaging (MRI) to compare images of 18 astronauts' brains before and after missions of long duration, involving stays on the International Space Station, and of 16 astronauts' brains before and after missions of short duration, involving participation in the Space Shuttle Program. Images were interpreted by readers who were unaware of the flight duration. We also generated paired preflight and postflight MRI cine clips derived from high-resolution, three-dimensional imaging of 12 astronauts after long-duration flights and from 6 astronauts after short-duration flights in order to assess the extent of narrowing of CSF spaces and the displacement of brain structures. We also compared preflight ventricular volumes with postflight ventricular volumes by means of an automated analysis of T_1-weighted MRIs. The main prespecified analyses focused on the change in the volume of the central sulcus, the change in the volume of CSF spaces at the vertex, and vertical displacement of the brain.

RESULTS

Narrowing of the central sulcus occurred in 17 of 18 astronauts after long-duration flights (mean flight time, 164.8 days) and in 3 of 16 astronauts after short-duration flights (mean flight time, 13.6 days) ($P<0.001$). Cine clips from a subgroup of astronauts showed an upward shift of the brain after all long-duration flights (12 astronauts) but not after short-duration flights (6 astronauts) and narrowing of CSF spaces at the vertex after all long-duration flights (12 astronauts) and in 1 of 6 astronauts after short-duration flights. Three astronauts in the long-duration group had optic-disk edema, and all 3 had narrowing of the central sulcus. A cine clip was available for 1 of these 3 astronauts, and the cine clip showed upward shift of the brain.

CONCLUSIONS

Narrowing of the central sulcus, upward shift of the brain, and narrowing of CSF spaces at the vertex occurred frequently and predominantly in astronauts after long-duration flights. Further investigation, including repeated postflight imaging conducted after some time on Earth, is required to determine the duration and clinical significance of these changes. (Funded by the National Aeronautics and Space Administration.)

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Microgravity during spaceflight occurs when the force of gravity is unbalanced and the net force becomes so weak that virtual weightlessness results. The effects of microgravity on the brain have received attention in relation to a syndrome involving optic-disk edema and elevated intracranial pressure[1] in astronauts returning from the International Space Station. The National Aeronautics and Space Administration (NASA) coined the phrase "visual impairment and intracranial pressure [VIIP] syndrome" to describe this constellation of signs and symptoms,[1-4] but the cause of the syndrome and the associated changes in brain structure have not been studied extensively.

Our group has previously analyzed magnetic resonance images (MRIs) of the brains of persons undergoing long-term bed rest in a head-down tilt position, which is an Earth-based analogue of microgravity.[5] Maintaining this position for a long period of time has been associated with upward and posterior brain shift, increased density of brain tissue at the vertex, contraction of adjacent extraaxial cerebrospinal fluid (CSF) spaces, and increased ventricular volume.[5] Assessment for these changes after spaceflight could provide insights into the neurophysiological and anatomical changes in the brain caused by spaceflight.

A previous study that compared MRIs of the brain before and after spaceflight quantitatively assessed images from 27 astronauts and showed a decrease in the volume of frontotemporal gray matter and an increase in the volume of the medial primary sensorimotor cortexes.[6] The volume of global brain CSF was unchanged, but neither localized changes in CSF spaces nor global brain displacement were evaluated.

Since the VIIP syndrome has occurred almost exclusively in astronauts after missions of long duration, we used MRI to assess brain displacement, ventricular volume, and changes in CSF spaces before and after missions of long duration (involving stays at the International Space Station [ISS]) and compared these images with images obtained from astronauts after missions of short duration (involving the Space Shuttle Program). This analysis incorporated cine clips of pairs of high-resolution static images in order to make subtle displacements more apparent.

METHODS

STUDY DESIGN

Data for this observational study were acquired prospectively and analyzed retrospectively. All data were provided by the NASA Lifetime Surveillance of Astronaut Health Program. The study was approved by the institutional review boards at the NASA Johnson Space Center and the Medical University of South Carolina. All participants provided written informed consent for the use and publication of their data. NASA reviewed the manuscript and the videos, which preserve the astronauts' anonymity and are in compliance with the privacy standards of the NASA Astronaut Office.

PARTICIPANTS

A total of 35 astronauts underwent MRI of the brain before and after spaceflight. One astronaut underwent preflight and postflight imaging on two different MRI scanners and was excluded from the study. The cohort described here consisted of 34 astronauts, 18 of whom participated in long-duration missions (long-duration group) on the ISS and 16 of whom participated in short-duration missions (short-duration group) in space shuttle flights. Preflight MRIs were obtained at a mean of 287.5 days (range, 18 to 627) before launch. Postflight imaging occurred at a mean of 6.7 days (range, 1 to 20) after spaceflight. A total of 31 participants had traveled on previous missions and therefore had been exposed to microgravity before undergoing their preflight MRIs. The study design is summarized in Figure 1.

IMAGING PROTOCOLS AND INTERPRETATION OF IMAGES

MRIs were performed at 3 Tesla, without the administration of contrast material, on a Philips Intera system (Philips Medical Systems) in 13 astronauts and on a Siemens Verio system (Siemens Healthcare) in 21 astronauts. The Philips imaging protocol included T_2-weighted, multiplanar imaging (slice thickness, 3 to 4 mm), and the Siemens protocol included three-dimensional T_1-weighted and T_2-weighted imaging, which allowed for reconstruction of the slices in any plane (slice thickness, ≤1 mm).

On evaluation of T_2-weighted imaging, the

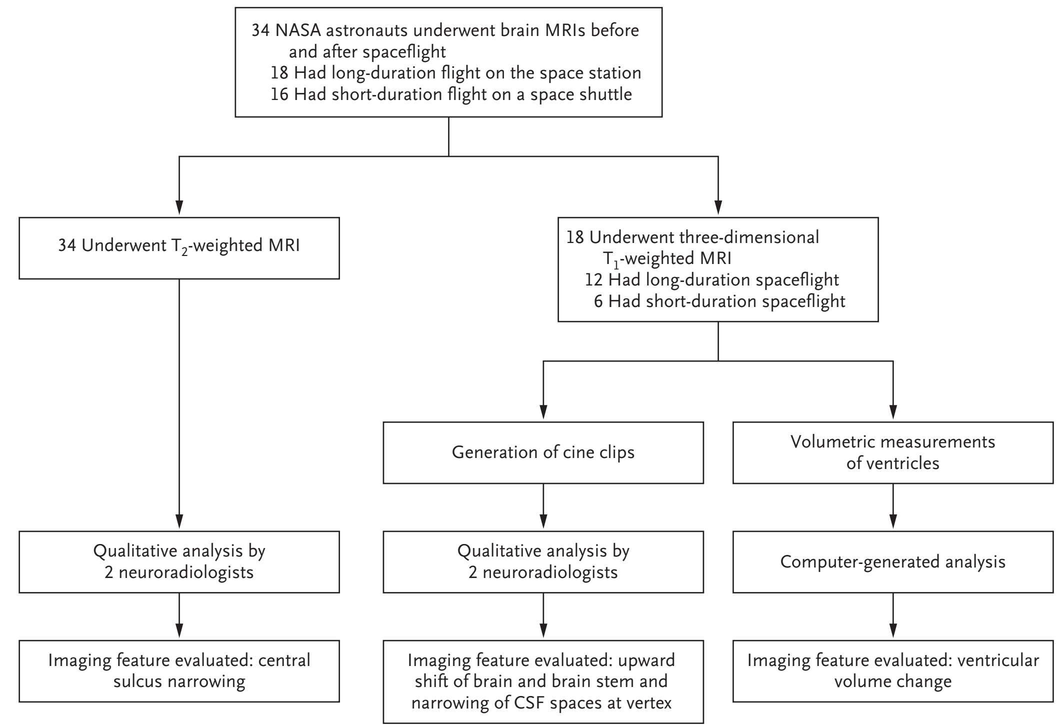

Figure 1. Study Design.

main prespecified analysis concerned change in the dimension of the central sulcus — whether it had widened, was unchanged, or had narrowed after spaceflight. Secondary features that were not prespecified but were considered areas of interest included change in the dimensions of the calcarine sulcus and supravermian cistern, the width of the third ventricle as measured on axial images, and the position of the cerebellar tonsils relative to the basion–opisthion line as measured on paired sagittal imaging. Measurements of the width of the third ventricle and the position of the cerebellar tonsils were made with the use of the measuring tool in the image-display software (Agfa Healthcare). All T_2-weighted images were evaluated by two neuroradiologists who were unaware of flight durations and the order of presentation of preflight and postflight imaging. Masking of the images was facilitated by presenting MRIs from short- or long-duration flights in random sequence and presenting preflight and postflight scans for each participant in random sequence. If there was an lack of concordance between readers, the readers were required to reach consensus for the final reading.[7] The quantitative measures (width of the third ventricle and position of the cerebellar tonsil) are presented as the mean (±SD) of the readers' measurements.

Cine clips were used for additional analysis of a subgroup of study participants. These clips were generated from pairs of high-resolution, three-dimensional, T_1-weighted sequences that were available for the 21 astronauts whose MRI studies were obtained in accordance with the Siemens protocol. The necessary postflight three-dimensional sequences were not performed for 1 astronaut in this group and the sequences for 2 others were degraded by motion. Therefore, cine clips were available for analysis from 18 astronauts (12 long-duration flights and 6 short-duration flights). The paired cine clips were compared by aligning an individual astronaut's postflight MRI with the preflight MRI, allowing the reader to toggle between the two images in identical planes to facilitate a qualitative impression of change in anatomical relationships (for further details

Table 1. Demographic Characteristics of the Participants.*

Characteristic	Long-Duration Flight	Short-Duration Flight	Mann–Whitney U Test	
			U	P Value
Spaceflight duration (days)	164.8±18.9	13.6±1.7	0	<0.001
Age at launch (yr)	48.6±4.7	47.5±3.0	117.0	0.37
Previous spaceflight experience (days)	34.5±56.4	69.8±94.5	191.5	0.1
Time between preflight MRI and launch (days)	424.6±183.3	133.3±112.4	31.0	<0.001
Time between return and postflight MRI (days)	4.2±2.2	9.6±7.5	203.5	0.04

* Plus–minus values are means ±SD.

on these methods, see the Supplementary Appendix, available with the full text of this article at NEJM.org). To avoid confounding factors in the interpretation of anatomical changes, including differences in participant position within the scanner and differences in alignment between pairs of images, the outer table of the skull was used as a fixed reference (unlike weight-bearing bone, calvarial volume does not change in microgravity[8]). The cine clips were reviewed by two neuroradiologists to assess the following prespecified features: presence or absence of upward shift of the brain and narrowing of CSF spaces at the vertex. Other features that were evaluated but were not prespecified were cerebral aqueduct rotation (defined as any displacement or distortion of the aqueduct between preflight and postflight MRIs), uplifting of the optic chiasm, and stretching of the pituitary stalk.

Volumetric Ventricular Measurements

The percentage change in the total volume of the ventricular system (lateral, third, and fourth ventricles) between preflight and postflight was quantified in the 18 participants for whom high-resolution, three-dimensional, T_1-weighted sequences were obtained. These sequences were analyzed with the use of the open-access Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library, available at http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/. (For details, see the Supplementary Appendix.) The process of analyzing the sequences incorporated the following automated steps: brain extraction (removal of the skull and extracranial soft tissues), registration, and segmentation to obtain ventricular volumes.

Clinical Evaluation

All astronauts underwent ophthalmologic examination on return from space. Lumbar puncture was performed in those with optic-disk edema in order to measure opening pressure.

Statistical Analysis

We conducted Mann–Whitney U tests for independent samples (two-sided exact P value) to compare the two groups of astronauts on the basis of age, previous spaceflight experience, time in space, and time between preflight and postflight MRI examinations. Fisher's exact tests were used to test the presence or absence of narrowing in specific CSF spaces in the short-duration and long-duration groups (two-sided exact P value, without corrections for multiple comparisons) and to evaluate the cine clips for the two groups for the presence or absence of brain movement. Independent sample Student's t-tests were used to evaluate differences in the two groups of astronauts on the basis of preflight-to-postflight changes in the width of the third ventricle, position of the cerebellar tonsil, and total volume of the ventricular system. Statistical analyses were conducted with the use of SPSS software, version 23 (IBM).

Results

Characteristics of Astronauts and Flights

Of the 34 astronauts, 28 were men (who had participated in 14 flights of long duration and 14 of short duration) and 6 were women. The mean time in orbit was 164.8±18.9 days for the long-duration group and 13.6±1.7 days for the short-duration group (Table 1). There were no significant differences in the age or previous spaceflight experience between the two groups of astronauts. There was a significantly longer interval between baseline imaging and launch in the long-duration group than in the short-duration group (mean number of days, 424.6 vs. 133.3; $P<0.001$). Astronauts who had long-duration flights underwent scanning sooner after their return to Earth than those who had short-duration flights (mean number of days, 4.2 vs. 9.6; $P=0.04$). Table S1 in the Supplementary Appendix shows the duration of flight (short vs. long), presence of optic-disk edema, and the main findings on brain imaging for each astronaut.

Changes in CSF Regional Volume on Static Images

Videos showing changes to the brain after long-duration spaceflight are available at NEJM.org

The consensus interpretation of the two neuroradiologists, which was based on the qualitative assessment of preflight and postflight paired images, was that there was narrowing of the central sulcus in 20 of 34 astronauts (59%). The supravermian cistern was narrowed in 7 of 34 astronauts (21%) and the calcarine sulcus was narrowed in 5 of 34 (15%) in comparisons of preflight and postflight paired images. The narrowing of CSF spaces occurred at a significantly higher rate in the long-duration group than the short-duration group; this finding applied to CSF spaces in the central sulcus (17 of 18 [94%] vs. 3 of 16 [19%], $P<0.001$) (Fig. 2), the supravermian cistern (7 of 18 [39%] vs. 0 of 16, $P=0.008$), and the calcarine sulcus (5 of 18 [28%] vs. 0 of 16, $P=0.046$). The interobserver agreement between the two neuroradiologists' readings (before instances in which consensus was required) was as follows: change in dimension of the central sulcus (the main imaging feature), 91% (31 of 34 paired images); the calcarine sulcus, 65% (22 of 34); and the supravermian cistern, 59% (20 of 34).

The mean increase in the width of the third ventricle after long-duration flights was 0.74 ± 0.56 mm, and that after short-duration flights was 0.11 ± 0.23 mm ($P<0.001$; equal variances not assumed). The mean upward movement of the cerebellar tonsils relative to the basion–opisthion line after long-duration flights was 1.08 ± 0.94 mm, and that after short-duration flights was 0.10 ± 0.87 mm ($P=0.046$).

Cine-Clip Findings

Cine clips were available for 12 astronauts in the long-duration group and 6 astronauts in the short-duration group. In their consensus readings of the images from these 18 astronauts, the two neuroradiologists reported an upward shift of the brain and brain stem in 12 (67%), narrowing of CSF spaces at the vertex in 13 (72%), rotation of the cerebral aqueduct in 12 (67%), stretching of the pituitary stalk in 11 (61%), and uplifting of the optic chiasm in 6 (33%). These findings were significantly more common in the long-duration group than in the short-duration group: upward shift of the brain and brain stem, 12 astronauts (100%) versus none ($P<0.001$) (Videos 1 and 2); narrowing of CSF spaces at the vertex, 12 (100%) versus 1 (17%) ($P<0.001$) (Videos 3 and 4); rotation of the aqueduct, 12 (100%) versus none ($P<0.001$) (Video 5); stretching of the pituitary stalk, 11 (92%) versus none ($P<0.001$) (Video 6). Upward displacement of the optic chiasm occurred in 6 (50%) of the long-duration astronauts versus none of the short-duration astronauts, a finding that approached statistical significance ($P=0.054$) (Video 6). The interobserver agreements of the two neuroradiologists' readings were 83% (15 of 18 astronauts) for both main prespecified cine clips imaging features of upward brain shift and narrowing of CSF spaces at the vertex. The interobserver agreement for features that were not prespecified were 78% (14 of 18) for rotation of the aqueduct, 67% (12 of 18) for stretching of the pituitary stalk, and 61% (11 of 18) for uplifting of the optic chiasm.

Changes in Ventricular Volume

There was a significant difference in the mean increase in the total volume of the ventricular system after spaceflight in the long-duration group as compared with the short-duration group ($11\pm5.9\%$ vs. $0.04\pm1.87\%$, $P<0.001$). The percentage change from preflight to postflight ventricular volumes for each astronaut is provided in Table S1 in the Supplementary Appendix and is typified in Videos 7 and 8.

Correlations in Clinical Findings and Brain Images

Edema of the optic disks after spaceflight was found in three participants, all of whom had

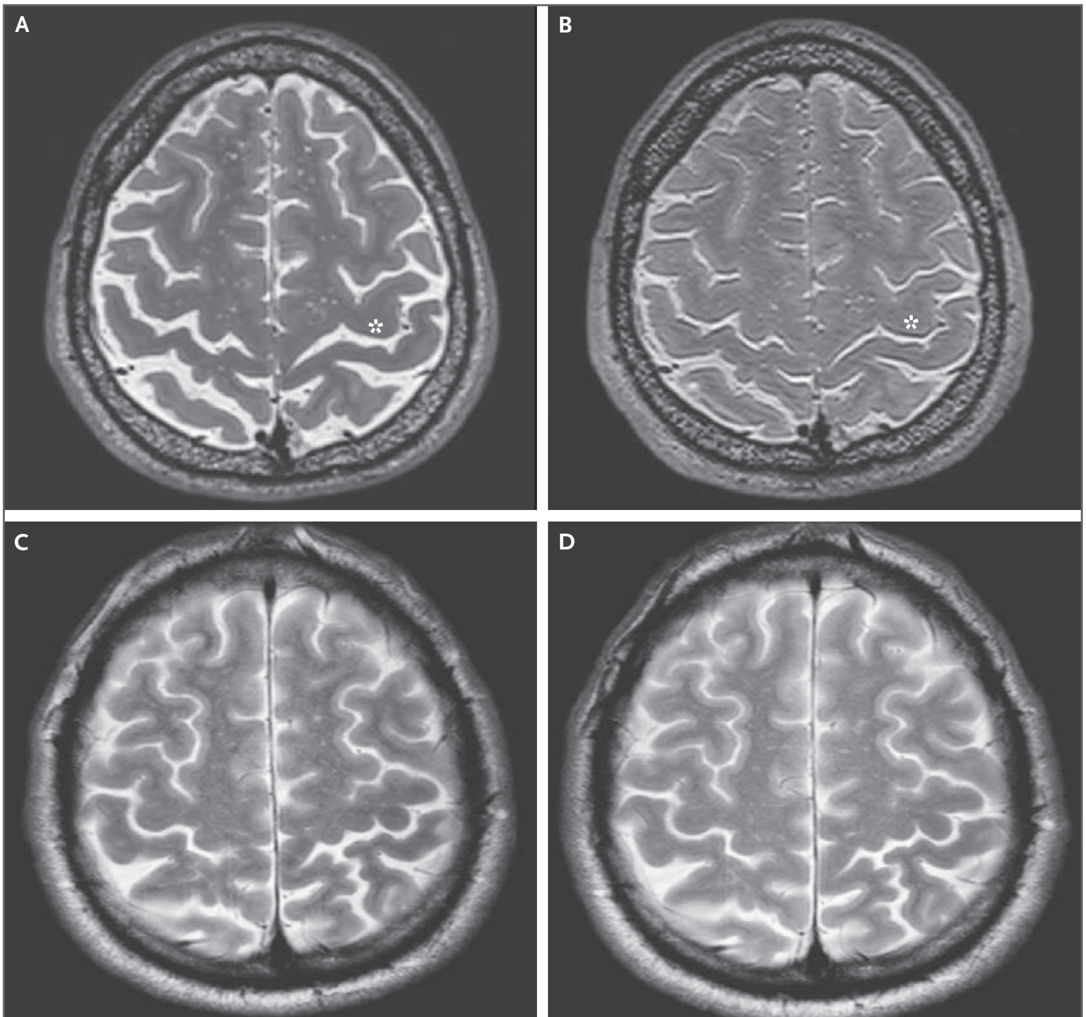

Figure 2. Representative Images.
Axial T_2-weighted images of the brain obtained before (Panel A) and after (Panel B) this astronaut had undergone long-duration spaceflight on the International Space Station (Participant 18). The astronaut presented with optic-disk edema and the visual impairment and intracranial pressure syndrome after spaceflight. Crowding of the sulci can be seen at the vertex. The gyrus (asterisk) is the precentral gyrus (primary motor cortex). Axial T_2-weighted images of the brain obtained before (Panel C) and after (Panel D) short-duration spaceflight on the space shuttle (Participant 5) show no change in the appearance of the sulci at the vertex. This postflight image was obtained on the second day after the astronaut's return to Earth.

participated in long-duration flights and had undergone lumbar puncture. Participant 18 underwent postflight MRI on day 6, and the CSF pressure that was measured on day 12 was 28 cm of water. Participant 19 (MRI on day 5 and lumbar puncture on day 8) had a CSF pressure of 18 cm of water. Participant 24 (MRI on day 6) had CSF pressures of 21.5 cm of water on day 7 and 16.25 cm of water on day 378. (Additional data on these participants are available in the Supplementary Appendix.)

All three astronauts with optic-disk edema had narrowing of the central sulcus when preflight and postflight MRIs were compared. A cine clip was available for one of these participants and showed upward shift of the brain, narrowing of CSF spaces at the vertex, stretching of the pituitary stalk, and rotation of the cerebral aqueduct postflight.

Discussion

In this study comparing MRIs obtained from astronauts before and after spaceflight, the prespecified outcomes of narrowing of the central sulcus occurred in 17 of 18 (94%) astronauts in the long-duration group and in 3 of 16 (19%) astronauts in the short-duration group. Among the 12 astronauts in the long-duration group and the 6 astronauts in the short-duration group for whom there were cine clips, upward shift of the brain occurred in all 12 of those in the long-duration group and in none of those in the short-duration group, and narrowing of CSF spaces at the vertex occurred in all 12 of those in the long-duration group and in 1 of 6 (17%) of those in the short-duration group. These findings occurred independently of the previous flight experience of the astronauts.

One explanation for these findings is upward displacement of the cerebral hemispheres and concurrent ventricular enlargement. It is also possible that an increase in the volume of the sensorimotor cortex, previously reported in astronauts,[6] contributed to narrowing of the central sulcus. However, this increase in sensorimotor cortical volume has been attributed to neuroplasticity during adaptation to the microgravity environment[6] with expected changes in cortical thickness of less than 1 mm,[9,10] an observation that would be insufficient to explain the reduction of several millimeters in CSF spaces at the vertex in the astronauts in our study.

Enlargement of the ventricular system was observed after long-duration spaceflight in this study, which corroborates findings from another report involving 16 astronauts.[11] We hypothesize that rotation of the cerebral aqueduct, which was present in all astronauts in the long-duration group for whom cine clips were available, may have led to increased resistance to CSF outflow from the third ventricle. A similar feature of altered CSF flow velocities in the cerebral aqueduct has been reported in astronauts after long-duration flights.[12]

Virtually all previous instances of the VIIP syndrome after spaceflight have occurred after long-duration flights.[3] Optic-disk edema and CSF pressures that were mildly elevated or at the high end of the normal range developed in three astronauts in the long-duration group. Although all three of these astronauts had narrowing of the central sulcus and one astronaut for whom cine clips were available had upward brain shift and narrowing of CSF spaces at the vertex, these findings were also present in many of the astronauts in the long-duration group in whom optic-disk edema did not develop (Table S1 in the Supplementary Appendix). Therefore, in our cohort, the relationship between findings on MRI of the brain and the VIIP syndrome was inconsistent. We suggest that upward brain shift with tissue crowding at the vertex may compress adjacent venous structures or obstruct arachnoid granulations along the superior sagittal sinus, causing obstruction of the CSF and venous outflow, thereby elevating intracranial pressure and resulting in papilledema.[13] Assessment of this hypothesis will require the addition of high-resolution cerebral venous imaging to preflight and postflight MRI examinations. The occurrence of optic-disk edema with brain shifts is also influenced by anatomical features, such as the cup:disk ratio.

The limitations of our study include the use of two different MRI systems, our ability to generate cine clips only in a subgroup of participants, the small number of astronauts who had not flown before, and the absence of long-term follow-up imaging to determine whether the structural changes in the brain returned to preflight baseline levels. Although the interval between preflight and postflight imaging was shorter in the short-duration group than in the long-duration group (a mean difference of 438 days), it is unlikely that any difference in the natural aging of the two groups explains the narrowing of the central sulcus and the CSF spaces at the vertex. The loss of brain volume associated with normal aging is approximately 0.2% per year.[14] Moreover, this loss would be expected to manifest as enlargement of the CSF spaces at the vertex, yet the opposite occurred because of upward shift of the brain. In the long-duration group, images were obtained an average of 4 days after the return to Earth, as compared with 9 days in the short-duration group, a difference that raises the possibility that structural changes in the brain that occurred during short-duration flight normalized before the postflight images were obtained. However, four astronauts in the short-duration group from whom images were obtained fewer than 4 days postflight did not have the changes on MRI that were identified in the long-duration group. Further evidence supporting the validity of our main prespecified imaging findings in the long-duration group is that these findings are similar to the structural changes in the brain that we previously described after long-duration bed rest.[5]

In conclusion, we observed an upward shift of the brain, narrowing of the central sulcus, and narrowing of CSF spaces at the vertex in most of the astronauts in this study who had had long-duration flights. These changes occurred much less frequently after short-duration flights. Our findings support the need for repeated longitudinal imaging over a longer period after spaceflight and the incorporation of advanced MRI techniques into NASA imaging protocols[15-17] to determine the persistence of these changes and their relationship to the VIIP syndrome. Determining the cause of the VIIP syndrome will be important in planning longer-duration spaceflights, such as a crewed mission to Mars.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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