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Spaceflight-induced changes in white matter hyperintensity burden in astronauts

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ABSTRACT

Objective: To assess the effect of weightlessness and the respective roles of CSF and vascular fluid on changes in white matter hyperintensity (WMH) burden in astronauts.

Methods: We analyzed prespaceflight and postspaceflight brain MRI scans from 17 astronauts, 10 who flew a long-duration mission on the International Space Station (ISS) and 7 who flew a short-duration mission on the Space Shuttle. Automated analysis methods were used to determine preflight to postflight changes in periventricular and deep WMH, CSF, and brain tissue volumes in fluid-attenuated inversion recovery and high-resolution 3-dimensional T1-weighted imaging. Differences between cohorts and associations between individual measures were assessed. The short-term reversibility of the identified preflight to postflight changes was tested in a subcohort of 5 long-duration astronauts who had a second postflight MRI scan 1 month after the first postflight scan.

Results: Significant preflight to postflight changes were measured only in the long-duration cohort and included only the periventricular WMH and ventricular CSF volumes. Changes in deep WMH and brain tissue volumes were not significant in either cohort. The increase in periventricular WMH volume was significantly associated with an increase in ventricular CSF volume (ρ = 0.63, p = 0.008). A partial reversal of these increases was observed in the long-duration subcohort with a 1-month follow-up scan.

Conclusions: Long-duration exposure to microgravity is associated with an increase in periventricular WMH in astronauts. This increase was linked to an increase in ventricular CSF volume documented in ISS astronauts. There was no associated change in or abnormal levels of WMH volumes in deep white matter as reported in U-2 high-altitude pilots. ***Neurology*® 2017;89:1–5**

GLOSSARY

FLAIR = fluid-attenuated inversion recovery; **GM** = gray matter; **iNPH** = idiopathic normal pressure hydrocephalus; **ISS** = International Space Station; **PWMH** = periventricular white matter hyperintensities; **WM** = white matter; **WMH** = white matter hyperintensities.

White matter [WM] hyperintensities (WMH) are regions of high image intensity on T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI. WMH are associated with a variety of etiologies, most commonly small vessel disease and infectious and inflammatory etiologies. The pathophysiology of WMH is multifactorial and may be of vascular origin (ischemia with loss of WM cellular elements and edema) or CSF origin (transependymal). WMH of CSF origin are located adjacent to the walls of the lateral ventricles and are referred to as periventricular WMH (PWMH). The prevalence of diffuse WMH increases with age, and diffuse WMH are uncommon in young people. Larger amounts of diffuse WMH reflect small vessel disease and are linked to cognitive impairment.[1] A significant increase of WMH burden was reported in high-altitude U-2 pilots compared to age-matched healthy controls.[2] The increased WMH were uniformly distributed throughout the brain and were likely related to microbubbles of predominantly nitrogen gas formed during low ambient pressure (hypobaria).[2] WMH burden was not associated with hours of flight and was present in both beginner and experienced pilots.[3] The WMH in the U-2 pilots were associated with a wide range of cognitive impairments, from

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complaints of slowed thought processes to severe confusion, unresponsiveness,[4] and permanent cognitive decline.[5]

Astronauts are highly functional individuals who experience cognitive changes during spaceflight, sometimes referred to as space fog.[6] While the specific mechanism of spaceflight-induced cognitive changes is unclear, very little is known of the effect of weightlessness on WMH. Weightlessness affects primarily the cardiovascular system through cephalad shift of blood and vascular fluid toward the upper part of the body, causing puffy faces and what has been called chicken legs.[7] Another important effect of long-duration exposure to microgravity is ocular structural changes and visual impairment, which are linked to an increase in ventricular and orbital CSF volumes without an increase in brain tissue vascular fluid content.[8] We analyzed brain MRI scans obtained before and after short- and long-duration spaceflight to assess the effect of microgravity on WMH burden. In addition, we tested for associations between preflight to postflight changes in WMH burden and changes in the intracranial vascular and CSF. Finally, we tested the short-term reversibility of the identified changes.

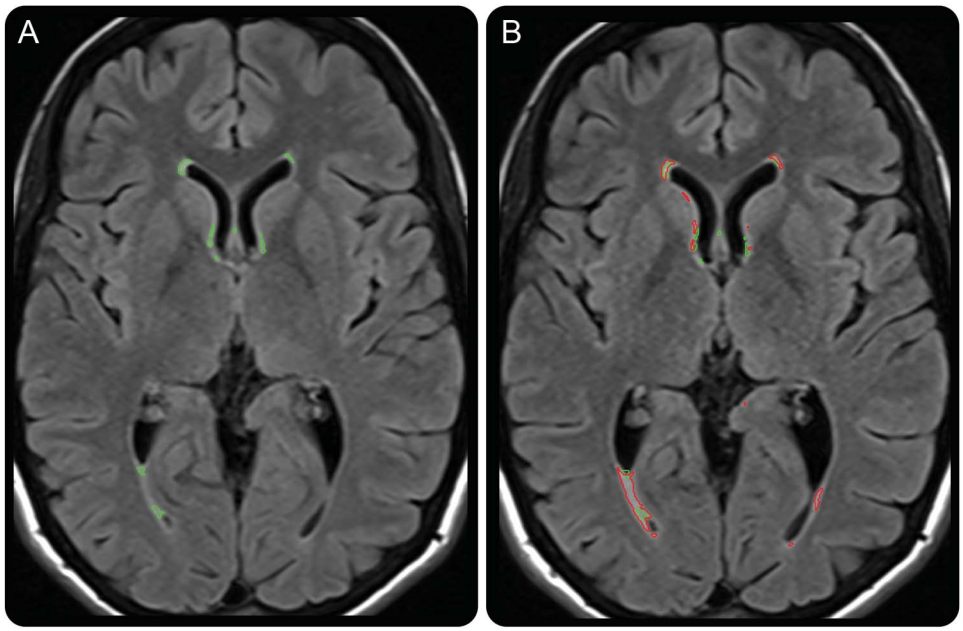
METHODS Standard protocol approvals, registrations, and patient consents. This study was approved by Johnson Space Center National Aeronautics and Space Administration institutional review board, and all participants provided written informed consent.

Participants and image acquisition. The study included data from 17 astronauts, 10 (mean ± SD age 46.2 ± 6.2 years) who flew a long-duration mission onboard the International Space Station (ISS) lasting on average 165 ± 19 days and 7 (age 47.7 ± 2.2 years) who flew a short-duration mission on the Space Shuttle lasting 14 ± 1.4 days. On average, a preflight MRI scan was performed nearly a year before departure, and the postflight scan occurred 6.1 ± 4 days after the return to Earth. Five of the 10 long-duration astronauts had a second postflight MRI scan ≈1 month after the first postflight scan. ~~Five of the 17 astronauts had previously flown a long-duration mission.~~

MRI scans of the brain were acquired with a 3T scanner (Verio, Siemens Healthcare, Malvern, PA) using a 32-channel head coil. Data included 3-dimensional T1-weighted magnetization-prepared rapid gradient echo and 2-dimensional T2-weighted FLAIR scans (figure 1). T1-weighted sequence parameters were repetition time/echo time of 1,900/2.3 milliseconds, inversion time of 900 milliseconds, flip angle of 9°, field of view of 25 × 25 cm, acquisition matrix of 256 × 256, and slice thickness of 1 mm. The axial FLAIR sequence parameters were repetition time/echo time of 9,000/85 milliseconds, inversion time of 2,500 milliseconds, flip angle of 150°, field of view of 22 × 22 cm, acquisition matrix of 256 × 192, and slice thickness of 3 mm. F1

Image analysis. Ventricular and cortical gray matter (GM) and WM volumes were automatically measured in the T1-weighted scans with the longitudinal stream in FreeSurfer, which is optimized for detecting small or subtle changes.[9] The periventricular and deep WMH volumes were segmented in the FLAIR images

Figure 1 FLAIR images acquired in an astronaut before and after long-duration spaceflight with the boundaries of the segmented PWMH regions overlaid on the images



(A) Preflight PWMH with boundaries shown in green. (B) Postflight PWMH with boundaries shown in red. FLAIR = fluid-attenuated inversion recovery; PWMH = periventricular white matter hyperintensities.

with a previously developed and validated method to measure changes in WMH in idiopathic normal pressure hydrocephalus (iNPH) after administration of acetazolamide.[10] Briefly, after skull removal and correction for bias field, the brain region was segmented into CSF and brain tissue classes. The mean (μ) and SD of the brain tissue image intensity were calculated and used to classify voxels having intensity greater than $\mu + 4 \times$ SD as WMH. The PWMH were then identified by coregistering the 3-dimensional T1-weighted image to the FLAIR image and projecting the periventricular mask region of voxels within 10 mm of the ventricular boundary.[11] WMH outside the periventricular regions were classified as deep WMH.

Statistical methods. The significance of differences in baseline measures and preflight to postflight changes between the short- and long-duration cohorts was assessed with an independent-sample *t* test. Associations between individual volumetric measures were tested with the Spearman correlation coefficients (ρ). Values of $p < 0.05$ were considered significant. Statistical analyses were performed with MATLAB Statistics and Machine Learning Toolbox (MathWorks Inc, Natick, MA).

RESULTS Mean and SD values of the preflight (baseline) and preflight to postflight changes in periventricular and deep WMH, ventricular CSF, and cortical GM and WM volumes for the short- and long-duration astronauts are listed in the table. At baseline, no significant differences in these measures were found between the 2 cohorts. In addition, no significant differences were found between the 5 astronauts who had previously flown a long-duration mission and the 12 astronauts who did not.

Preflight to postflight changes in PWMH and ventricular CSF volumes were significant only in the long-duration astronauts, with average increases of 0.21 mL (39%) and 3.1 mL (17%), respectively. In contrast, no significant differences were observed between the 2 cohorts in deep WMH volumes and GM and WM brain tissue volumes. In the long-duration subcohort, the 1-month follow-up scan demonstrated partial reversal of the increases in PWMH and ventricular CSF volume, with average reductions of 65% and 36%, respectively.

Scatterplots of the relationships between the preflight to postflight changes in WMH, ventricular CSF volume, and GM and WM brain tissue volumes are shown in figure 2. The only significant association was between the changes in PWMH and the ventricular CSF volume.

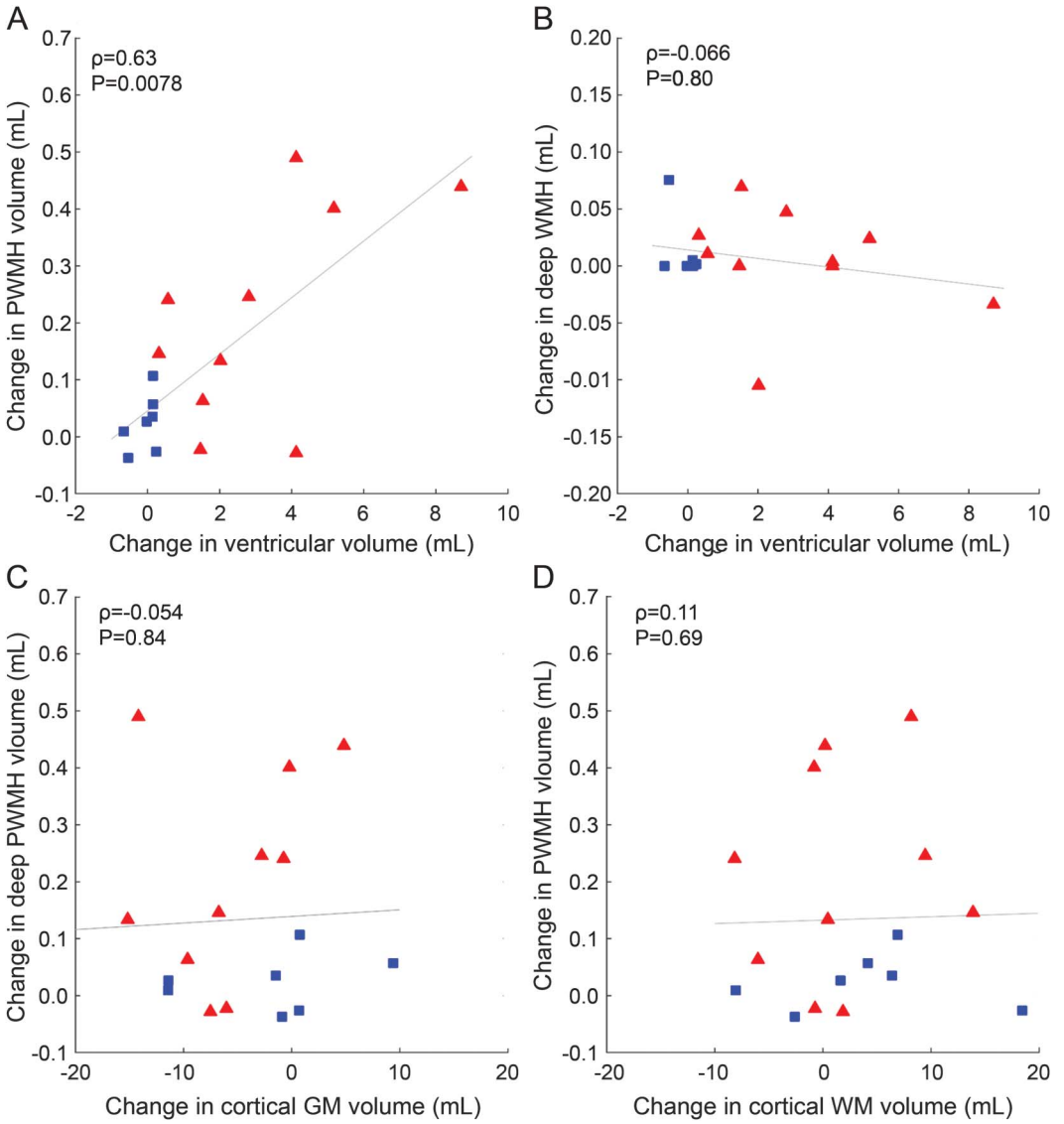
DISCUSSION As expected, preflight WMH volume for all astronauts was very small and likely not clinically relevant. A statistically significant preflight to postflight increase in WMH was measured in the ISS astronauts who flew long-duration mission, while no changes were detected in the Space Shuttle astronauts who flew short-duration mission. In contrast to the U-2 pilots who demonstrated increased WMH throughout the brain, the increased

Table Mean and SD of preflight and preflight to postflight changes in WMH and brain tissue volumes

	Preflight baseline					Preflight to postflight changes				
	PWMH volume, mL	Deep WMH volume, mL	Ventricular CSF volume, mL	GM volume, mL	WM volume, mL	Change in PWMH volume, mL	Change in deep WMH volume, mL	Change in ventricular CSF volume, mL	Change in GM volume, mL	Change in WM volume, mL
Short- duration (n = 7)	0.33 ± 0.36	0.01 ± 0.01	19.8 ± 15.3	486 ± 43.5	505 ± 42.2	0.02 ± 0.05	0.01 ± 0.03	−0.07 ± 0.4	−2.0 ± 7.3	3.8 ± 8.3
Long-duration (n = 10)	0.54 ± 0.36	0.15 ± 0.26	18.2 ± 6.4	483 ± 35.3	495 ± 62.1	0.21 ± 0.19	0.00 ± 0.05	3.1 ± 2.5	−5.8 ± 6.3	1.8 ± 6.5
p Value	0.24	0.11	0.81	0.87	0.69	0.01[a]	0.69	0.003[a]	0.29	0.61

Abbreviations: GM = gray matter; PWMH = periventricular white matter hyperintensity; WM = white matter; WMH = white matter hyperintensity.
[a] Significant.

Figure 2 Associations between change in volumetric measures in short- and long-duration astronauts



Scatterplots displaying the association between (A) change in PWMH and ventricular CSF volumes, (B) change in deep WMH and ventricular CSF volumes, (C) change in PWMH and GM volume, and (D) changes in PWMH and WM volume. Squares and triangles represent short- and long-duration astronauts, respectively. GM = gray matter; PWMH = periventricular white matter hyperintensities; WM = white matter; WMH = white matter hyperintensities.

WMH in the ISS astronauts occurred only in the periventricular regions with no observed changes in deep brain regions.

The increase in PWMH is significantly associated with the increase in ventricular CSF volume that occurs during long duration of weightlessness, and it is at least partially reversible on return to normal gravity. The increase in the ventricular CSF volume likely promotes an increase in transependymal CSF movement from the ventricles into the parenchyma, leading to the increase in PWMH.

Reversal of PWMH and a significant association between changes in PWMH and ventricular CSF volumes have been previously reported in iNPH.[10] The reversal of PWMH in iNPH occurred after administration of low-dose acetazolamide, which reduces CSF formation. In astronauts, PWMH increases during long-duration exposure to microgravity in response to an increase in ventricular CSF volume.[8] On return to gravity on Earth, the increased PWMH and ventricular volumes gradually decrease, although no long-term follow-up scans were available to determine whether they return to baseline values.

The absence of an increase in deep WMH is consistent with the fact that the ISS astronauts are not exposed to hypobaria (ISS is kept at atmospheric pressure), as were the U-2 pilots. However, the ISS astronauts are exposed to periods of increased CO_2 levels,[12] yet they do not demonstrate an increase in

deep WMH. These findings are consistent with findings in patients with sleep apnea demonstrating that WMH are associated with hypoxemia but not hypercarbia.[13] An increase in deep WMH was not observed even in the 7 ISS astronauts who were classified as having visual impairment intracranial pressure syndrome.[8] The lack of diffuse WMH in the ISS astronauts implies that the visual impairment intracranial pressure syndrome is likely not associated with a large increase in intracranial pressure because this would have led to reduced perfusion pressure and ischemia. Our findings further confirm that the cognitive disturbances reported in ISS astronauts are not associated with deep WMH.

Limitations of our study include the retrospective design and the relatively low-resolution FLAIR images in the slice direction, which leads to an increase in volumetric measurement error due to the partial volume effect, and the small number of astronauts. Regardless of these limitations, the increase in PWMH and its correlation with the increase in ventricular volume in the long-duration cohort reached statistical significance.

Long-duration exposure to microgravity is associated with a small but significant increase in PWMH without changes in the deep WMH. This increase is significantly associated with the increase in ventricular CSF volume that occurs during a long duration of weightlessness and is at least partially reversible on return to normal gravity, thereby suggesting causality. The lack of formation of deep WMH suggests that the cognitive performance changes reported in long-duration astronauts are not related to WMH burden.

AUTHOR CONTRIBUTIONS

Noam Alperin: study design, acquisition and interpretation of data, study supervision, manuscript editing. Ahmet M. Bagci: analysis and interpretation of data, statistical analysis, manuscript editing. Sang Lee: manuscript editing.

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DISCLOSURE

N. Alperin is a shareholder in Alperin Noninvasive Diagnostics. A. Bagci and S. Lee report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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