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Optic Nerve Length before and after Spaceflight

Anders Wåhlin, PhD,[1,2] Petter Holmlund, PhD,[1] Abigail M. Fellows, BS,[3] Jan Malm, MD, PhD,[4] Jay C. Buckey, MD,[3] Anders Eklund, PhD[1,2]

Purpose: The spaceflight-associated neuro−ocular syndrome (SANS) affects astronauts on missions to the International Space Station (ISS). The SANS has blurred vision and ocular changes as typical features. The objective of this study was to investigate if microgravity can create deformations or movements of the eye or optic nerve, and if such changes could be linked to SANS.

Design: Cohort study.

Participants: Twenty-two astronauts (age 48 ± 4 years).

Methods: The intervention consisted of time in microgravity at the ISS. We co-registered pre- and post-spaceflight magnetic resonance imaging (MRI) scans and generated centerline representations of the optic nerve. The coordinates for the optic nerve head (ONH) and optic chiasm (OC) ends of the optic nerve were recorded along with the entire centerline path.

Main Outcome Measures: Optic nerve length, ONH movement, and OC movement after time in microgravity.

Results: Optic nerve length increased (0.80 ± 0.74 mm, $P < 0.001$), primarily reflecting forward ONH displacement (0.63 ± 0.53 mm, $P < 0.001$). The forward displacement was positively related to mission duration, preflight body weight, and clinical manifestations of SANS. We also detected upward displacement of the OC (0.39 ± 0.50 mm, $P = 0.002$), indicative of brain movement, but this observation could not be linked to SANS.

Conclusions: The spaceflight-induced optic nerve lengthening and anterior movement of the ONH support that SANS is caused by an altered pressure difference between the brain and the eye, leading to a forward push on the posterior of the eye. Body weight is a potential contributing risk factor. Direct assessment of intracranial pressure in space is required to verify the implicated mechanism behind the ocular findings in SANS. *Ophthalmology 2021;128:309-316 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.aaojournal.org.

Subjective visual symptoms, including blurred vision, have been reported in up to 60% of astronauts during and after long-duration missions at the International Space Station (ISS).[1] Corresponding structural eye changes have been found, including optic disc edema, globe flattening, and choroidal folds.[1-5] Spaceflight-associated neuro-ocular syndrome (SANS) is a major medical obstacle in space medicine. Although to date, the visual changes have been correctable with glasses, the cause is unknown, as is the risk it poses for longer journeys in space, such as planned trips to Mars. Suggested risk factors for developing SANS are an increased preflight body weight and differences in 1-carbon metabolism.[6] While the ophthalmological symptomology of SANS resembles that of the neurologic syndrome idiopathic intracranial hypertension (IIH), a paradoxical difference is that IIH typically features headaches and SANS does not. That IIH and SANS share similar eye findings but not the brain (headaches) symptoms suggests that the underlying causes for the findings may be partly different.

One potential explanation for SANS postulates an increase in intracranial pressure (ICP) due to the headward fluid shift that occurs in space.[2] In this theory, venous pressures in the head increase in space. This may lead to increased ICP that, via the optic nerve, exerts a force pushing on the posterior part of the eye. Furthermore, because of the microgravity environment on the ISS, the lowering of ICP seen when upright on Earth is absent.[7,8] An ICP constantly at supine levels could create a persistent force on the posterior part of the eye, which over time might lead to anterior movement of the optic nerve head (ONH) and globe flattening. One support for this theory is that in healthy individuals, optic disc edema has been shown to develop after 30 days of strict head-down bed rest, that is, simulated microgravity.[9]

Another potential explanation hypothesizes that an upward brain displacement leads to SANS.[10] Postflight magnetic resonance imaging (MRI) after long-duration spaceflight shows a superior shift of the brain, brain stem,

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and optic chiasm (OC).[11] This brain displacement may occur in space and cause an excessive structural load on the optic nerve, resulting in a mechanical stretch and a rearward shift of the optic nerve where it connects with the eye. This backward movement, combined with a restoration force from the dura mater, could produce globe flattening. In this scenario, the ONH would move posteriorly.[10]

In this work, we considered these 2 theories. The study included 22 astronauts examined with MRI before and after a stay at the ISS. We focused on the optic nerve as a structure that may reveal the mechanism underlying SANS and investigated postflight optic nerve length changes, as well as displacements of the ONH and OC and their relation to clinical manifestations of SANS.

Methods

Participants

The study approach is illustrated in Figure 1A to C, and subject specifics are shown in Table 1. The astronauts studied likely included many of the same individuals in the MRI study by Roberts et al.[11] Institutional Review Board (IRB)/Ethics Committee approval was obtained from the Committee for the Protection of Human Subjects (IRB) at Dartmouth College and the regional ethical review board in Umeå. The research was also approved by the IRB at NASA, and use of the data was approved by the Lifetime Surveillance of Astronaut Health program. The research adhered to the tenets of the Declaration of Helsinki.

This interventional study included active space station astronauts (N = 22; aged 48 ± 4 years, 3 women). The intervention consisted of stays of varying lengths at the ISS. The average time in space was 109±75 days. To investigate effects related to time spent in microgravity, 2 subgroups were analyzed: I. short-duration missions (N = 8, mean spaceflight duration of 15 days) and II. long-duration missions (N = 14, mean spaceflight duration of 163 days). A baseline and a postflight follow-up MRI were collected to obtain the spaceflight-induced morphologic changes affecting the brain and orbit as well as the intracranial space.

The data on clinical features of SANS in the astronauts were acquired from the Lifetime Surveillance of Astronaut Health program. Fundus examination included assessments of postflight disc edema and choroidal folds. Five astronauts had such findings; all 5 had new choroidal folds, and 2 of these additionally had disc edema. We constructed a SANS group and a No SANS group that was separated based on the occurrence or absence of disc edema and choroidal folds (i.e., 1 group with disc edema or choroidal folds and 1 without any such findings).

Magnetic Resonance Imaging

All analyses within this study were performed based on T1-weighted 3D MPRAGE images obtained with a 3-Tesla Siemens Verio system (Siemens Healthcare, Erlangen, Germany). Imaging parameters were 0.9 mm isotropic resolution, repetition time 1900 ms, echo time 2.32 ms, flip angle 9, and inversion time 900 ms. Brain white matter volumetric segmentation was performed with the Freesurfer 6.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described.[12] Structural images were interpolated by a factor of 2 (yielding 0.45 mm isotropic resolution) to improve the ability to follow the center and the end points of the optic nerve accurately.

A 3-dimensional Bezier path was manually placed to obtain a centerline representation of the entire optic nerve from the ONH to the OC, using the software OsiriX (Pixmeo SARL, Bernex, Switzerland). Axial, sagittal, and coronal projections were considered simultaneously (Figs S1–S3, available at www.aaojournal.org). The ONH was defined as the visually identified intersection between the globe and a line centered in the optic nerve and pointing in the direction of the optic nerve, close to the lamina cribrosa (Fig S1, available at www.aaojournal.org). Likewise, the optic nerve end in the OC was defined by the visually identified intersection of an OC waistline in the coronal plane with a line centered in the optic nerve, pointing in the direction of the optic nerve (Fig S3, available at www.aaojournal.org). The coordinates for the ONH and OC ends of the optic nerve were recorded along with the entire path of the centerline. Optic nerve length was defined as the entire path of the centerline.

Two operators (A.W. and P.H.) independently created centerline representations of the optic nerves. The operators were blinded to the pre- or postspaceflight conditions of the scans. An average of the 2 operators was used for all statistical analyses. The optic nerve centerline representation (e.g., Fig 1B) was reproducible as indicated by the intraclass correlation (ICC) between observers (2-way random effects, absolute agreement, and multiple rater/measurement) for the measurements of optic nerve length ($r = 0.97$ for preflight and $r = 0.95$ for postflight, respectively). The ICC calculated directly on the optic nerve length delta had a moderate ICC of 0.59. Tortuosity was calculated as the ratio between the optic nerve length and the Euclidian distance between the ONH and OC.

To examine potential pre- to postflight shifts in the recorded coordinates of the ONH and OC ends of the optic nerve in relation to the skull, a reference point–based co-registration was performed.[13] This was achieved by visually identifying and matching features in the bone of the skull. In total, 4 reference points were placed on the baseline and follow-up scans (placed while simultaneously viewing both scans).

Coordinates of co-registered anterior and posterior end points were averaged between left and right optic nerves. This operation canceled the ability to detect lateral left-right movements of the end points, but such shifts were not considered interesting because of anatomic constraints and the overall symmetry of the investigated anatomic system.

Statistics

From a statistical standpoint, our study is analogous to a "2-eye design" because both eyes of each astronaut were exposed to microgravity. In such settings, using an average of the measures obtained from the 2 eyes is recommended.[14] Therefore, optic nerve length change and ONH and OC displacements were averaged between the left and right sides. In addition, an average between the 2 operators was used in all subsequently described analyses.

Two-sided, paired-samples t tests were used to compare optic nerve length changes, ONH displacements, OC displacements, and tortuosity changes between the baseline and follow-up scans. This was done on the entire sample, as well as on subgroups divided by long- and short-term flights to investigate potential importance of the spaceflight duration. Pearson correlation coefficients and 2-sided P values were used to characterize internal relationships between the magnitudes of optic nerve length change, ONH displacement, and OC displacement.

As hydrostatic effects and tissue compressive forces (caused by the weight of the tissue) are removed in microgravity, preflight

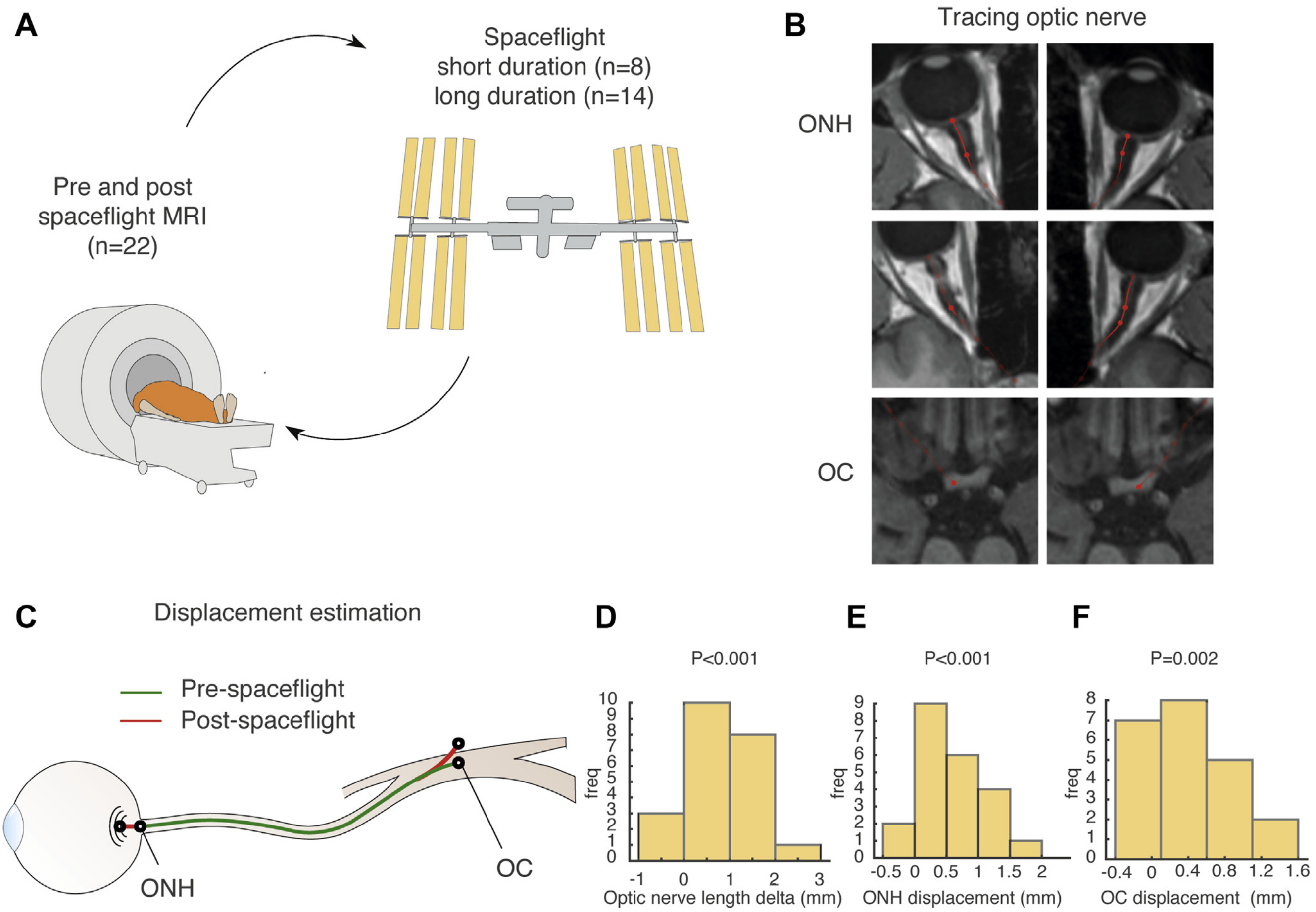

Figure 1. Overview of study approach and main results. **A,** Pre- and postspaceflight magnetic resonance imaging (MRI) scans were collected from astronauts and used to assess structural alterations to the optic nerve. **B,** A centerline representing the entire path of the optic nerve was drawn on pre- and postflight images. Projections in all cardinal directions were simultaneously considered in this process. Figures S1 to S3 (available at www.aaojournal.org) show more detailed examples. **C,** Rigid-body co-registration of pre- and postflight images enabled estimation of displacements of the optic nerve head (ONH) and optic chiasm (OC) ends of the optic nerve. **D,** Histogram of ONH displacement where positive values correspond to the anterior direction. **E,** Histogram of optic nerve length change where positive values correspond to length increase after spaceflight. **F,** Histogram of OC displacement where positive values correspond to the superior direction. OC = optic chiasm; ONH = optic nerve head.

body weight may relate to the severity of the ocular changes developed during spaceflight.[6] The relationship of ONH and OC displacement to mission duration and preflight weight was examined simultaneously using multiple linear regression. Optic nerve head and OC displacement were used as the response variable, and mission duration (short or long) and preflight weight were used as predictor variables. Two-sided P values were reported for analyses with multiple linear regression.

Next, we tested if ONH anterior displacement was more expressed in the SANS group compared with the No SANS group using 1-sided independent samples t test. This operation was repeated for the OC superior displacement.

We also investigated potential pre- to postflight differences in white matter volume using 2-sided paired t tests. Finally, we reported the Pearson correlation coefficient, with 2-sided P values, between ONH displacement, as well as OC displacement, and preflight intraocular pressure (IOP) (increased IOP may counteract flattening of the posterior globe and thus also ONH movement), change in axial length of the globe (a measure sensitive to globe flattening), and body mass index, weight, height, and age.

Results

The optic nerve was structurally altered after spaceflight (Table 2 and Fig 1C). After spaceflight, the average optic nerve length increased by 0.80 ± 0.74 mm ($P < 0.001$) (Fig 1D), without any apparent change in pre- to postflight optic nerve tortuosity ($P = 0.92$). The optic nerve length increase was primarily reflecting a structural alteration of the posterior part of the eye, as indicated by a strong correlation to spaceflight-induced anterior displacement of the ONH ($r = 0.80$, $P < 0.001$). In contrast, no correlation was found between optic nerve length increase and displacement of the OC ($r = 0.01$, $P = 0.96$). The average anterior displacement of the ONH was 0.63 ± 0.53 mm ($P < 0.001$), and the average upward shift of the OC was 0.39 ± 0.50 mm ($P = 0.002$) (Fig 1E–F). We found no significant movement in any other direction for the ONH or the OC ends ($P > 0.05$).

Both flight duration ($P = 0.03$) and preflight body weight ($P = 0.03$) were related to ONH anterior displacement (Table S1, available at www.aaojournal.org). No such relationship could be observed for OC displacement. On a case level, 100% (14/14) of

Table 1. Subject Specifics

	Total (N = 22)
Age [yrs]	48 ± 4
Mission duration [days]	109 ± 75
Preflight seated intraocular pressure [mmHg]*	13.0 ± 2.0
Preflight weight [kg]	82.9 ± 11.3
Preflight height [cm]	175.8 ± 5.1
Preflight body mass index [kg/m^2]	26.8 ± 3.5
Time from preflight MRI to the day of flight [days]	387 ± 209
Time from landing to postflight MRI [days]	17 ± 44 (median 5.5)†
Accumulated time from previous missions [days]	61 ± 93

Data were acquired from the Lifetime Surveillance of Astronaut Health program. Values presented as mean ± SD.
SD = standard deviation.
MRI = magnetic resonance imaging.
*Mean of both eyes.
†Median presented because of 1 significant outlier.

the long-duration subgroup and 75% (6/8) of the short-duration subgroup had an anterior ONH movement. The corresponding numbers for the upward movement of the OC were 64% (9/14) and 75% (6/8).

Astronauts displaying features of SANS (n = 5) had almost twice as large ONH anterior displacement compared with astronauts without such clinical findings (0.98 ± 0.69 vs. 0.53 ± 0.45 mm, $P = 0.05$). No such difference was seen in OC displacement (0.50 ± 0.53 vs. 0.35 ± 0.50 mm, $P = 0.29$).

Because optic nerve elongation and optic nerve end displacements could stem from edema and represent a general increase in white matter volume, we performed a control analysis and found no difference in whole brain white matter volume between pre- and postflight images ($P = 0.43$). An overview of correlations between ONH and OC displacement and other physiologic variables is presented in Table 3.

Table 2. Changes in the Optic Nerve after Spaceflight

	Mean ± SD	*P* Value
ONH anterior movement [mm]		
• All	0.63 ± 0.53	<0.001
• Long duration flight	0.78 ± 0.56	<0.001
• Short duration flight	0.37 ± 0.36	0.02
OC upward movement [mm]		
• All	0.39 ± 0.50	0.002
• Long duration flight	0.34 ± 0.45	0.01
• Short duration flight	0.47 ± 0.60	0.06
Optic nerve length increase [mm]		
• All	0.80 ± 0.74	<0.001
• Long duration flight	0.98 ± 0.71	<0.001
• Short duration flight	0.49 ± 0.74	0.10
Optic nerve tortuosity change [%]		
• All	−0.0 ± 1.6	0.92
• Long duration flight	0.3 ± 0.9	0.26
• Short duration flight	−0.6 ± 2.3	0.46

OC = optic chiasm; ONH = optic nerve head; SD = standard deviation.

Discussion

Based on pre- and postflight MRIs from astronauts participating in missions on the ISS, we detected anterior displacement of the ONH, superior displacement of the OC, and an overall length increase of the optic nerve (Fig 1C). Of note, ONH displacement, but not OC displacement, was related to mission duration. The ONH displacement was greater in those with clinical manifestations and correlated with both overall optic nerve length increase and body weight. Taken together, these observations cannot be reconciled with a model where a structural load on the optic nerve by the superior brain movement pulls the eye deeper into its socket. Instead, they favor a mechanism driven by a pressure differential across the eye (i.e., lamina cribrosa), leading to an anterior push on the posterior part of the eye.

The ONH displacement seen in this study could be due to a net force causing elongation of the optic nerve and optic nerve sheath. Microgravity prevents the normal lowering of ICP that occurs in the upright posture on Earth resulting from hydrostatic effects within venous blood and cerebrospinal fluid. As people spend most of their time (∼2/3) in an upright position, the anticipated 24-hour average ICP in microgravity is probably higher than the 24-hour average on Earth.[7,8] Furthermore, although ICP has not been measured in space, postflight measurements indicate an elevation in some individuals.[2] This could further contribute to a pressure imbalance over the lamina cribrosa in weightlessness that accordingly produces a net forward force. The 24-hour average increase in ICP (compared with Earth) could also add elevated tension forces to the optic nerve sheath surrounding the intraorbital part of the nerve, thereby increasing its rigidity and causing an additional increase in this forward force. This effect also could be enhanced by a reduction in intraorbital pressure, due to the loss of compressive forces, further increasing the pressure difference over the optic nerve sheath. Kramer et al[5] revealed that astronauts postflight had an average elevation in optic nerve sheath diameter, supporting the hypothesis of a pressure imbalance in that subset of astronauts. Thus, an ICP near supine values,[8,15] an IOP closer to standing values,[16] as well as a lower intraorbital pressure are all factors that could contribute to a net forward force in microgravity. Over time, this force may lead to an optic nerve elongation and a flattening of the globe, which are seen in these data as forward movement of the ONH.

The anterior movement of the ONH and thus also the detected length increase of the optic nerve could potentially be an effect of prelaminar (i.e., retina, choroid) thickening instead of a forward movement of the lamina cribrosa. In a recent OCT study, retinal thickness proximal to the ONH was increased after long-duration spaceflight by an average of 0.021 mm, and peripapillary choroid thickness was increased by an average of 0.020 mm.[17] Together this adds to a 0.041 mm total thickness increase. Similar data were also presented by Patel et al.[18] Our detected displacement of the anterior tip of the optic nerve of 0.63 mm is thus

Table 3. Correlations between Optic Nerve Head and Optic Chiasm Displacements and Physiologic Parameters in the Full Sample

	Parameter	N	Correlation Coefficient r	P Value
ONH displacement	Preflight IOP	22	−0.25	0.27
	Change in axial length	18	−0.59	0.01
	Preflight BMI	22	0.29	0.18
	Preflight weight	22	0.39	0.07
	Preflight height	22	0.31	0.16
	Age	22	0.00	0.99
OC displacement	Preflight IOP	22	0.1	0.65
	Change in axial length	18	−0.28	0.26
	Preflight BMI	22	0.06	0.80
	Preflight weight	22	0.01	0.98
	Preflight height	22	−0.09	0.68
	Age	22	−0.19	0.39

Positive displacement is in the anterior direction for ONH and the superior direction for OC.
BMI = body mass index; IOP = intraocular pressure; OC = optic chiasm; ONH = optic nerve head.

15 times greater than the total thickness increase in prelaminar tissue estimated by Macias et al.[17] In addition, the positioning of the tip of the optic nerve was accomplished by visually identifying the intersection of a contour centered in the posterior wall and a line centered in the optic nerve and pointing in the direction of the optic nerve. This was possible because, in T1 weighted images, the vitreous body appears black, whereas a clear white rim representing the retina, choroid, and sclera is easily distinguishable. Therefore, by placing the posterior wall contour centered in this rim, only 50% of any thickness increase in the prelaminar structure will be propagated to our optic nerve length delta. Taking half of the total thickness increase in Macias et al's[17] study gives 0.021 mm, a potential measurement bias that appears negligible compared with our detected anterior shift and length increase. Therefore, although prelaminar thickness increases could bias our optic nerve length estimates, such prelaminar structural alterations cannot explain the ONH anterior displacement detected in the present study.

A focal pushing on the back of the eye is further supported by the reduction in axial length seen in this study and in the study by Macias et al.[17] The changes to the optic nerve are likely the primary event because the magnitudes of optic nerve lengthening (0.8 mm) and anterior movement of the ONH (0.63 mm) are substantially larger than the mean axial length shortening at fovea (0.08 mm), supporting the idea that there is a push at the ONH that creates an ONH-centered flattening detectable as a correlated minor axial length shortening at fovea.

Instead of resulting from an ICP chronically elevated above upright values, it could be speculated that the structural changes of the eye, and thus the ONH, could be due to increases in intra-orbital content outside the optic nerve sheath. Such an increase in content should give rise to the radiologic sign called "tenting," where the posterior globe acquires a cone-shaped appearance due to the firm attachment and stretch of the optic nerve.[19] We did not observe any signs of tenting in the investigated material.

We found that the ONH anterior movement was related to body weight, supporting a link to tissue compressive forces. The loss of tissue compressive forces is evident in the reduction of central venous pressure that is observed in space[6] and will be proportionally larger for heavier individuals. Intriguingly, ICP is directly linked to central venous pressure.[20] A reduction in venous pressure below supine values is thus contradicting an elevation of ICP or IOP above supine levels on Earth. Additionally, ICP measured directly during short-duration microgravity exposures also shows a reduction below supine values.[21] This paradox motivates further exploration of the complex interrelationships between central venous pressure, ICP, and IOP and how they are affected by gravity. The absolute value of ICP or IOP is likely not as important as the difference between them.

Our results may be further understood considering that the optic nerve is tethered within the optic canal, and so may not easily move as a unit.[22] The ONH movement may be primarily affected by the pressure environment within the globe, the orbit, and inside the optic nerve sheath, whereas the OC may reflect changes due to brain movement. This raises the possibility that different mechanisms underlie the ONH and OC displacement findings.

Although a general 24-hour average ICP increase in microgravity (similar to supine values on Earth) will create an abnormal trans-lamina cribrosa pressure difference that could be large enough to mechanically alter the optic nerve, the ICP specifically would still be relatively normal from an Earth perspective and does not cause brain-related symptoms. This could explain why SANS-affected astronauts do not present with the typical headaches of IIH. From an IIH perspective, this suggests that the elevated ICP is the cause for the neurologic symptoms in IIH patients, whereas the ophthalmic symptoms stem from IOP-ICP differences and the resulting mechanical push on the eye.

We measured whole brain white matter volume and detected no changes from pre- to postspaceflight. The interpretation of the optic nerve length increase and ONH displacement changes would be more complex if optic nerve length was directly altered by changes in the white matter (e.g., swelling). Indeed, postflight measurements suggest exposure to microgravity may produce changes in white matter microstructure.[23] Kramer et al[5] identified a central area of T2 hyperintensity in the optic nerve, but they interpreted it as centrally located perivascular connective tissue and nonmyelinated optic nerve fibers surrounded by myelinated axons, and they found no evidence of vasogenic edema in the brain. Furthermore, an optic nerve elongation caused by edema should have generated an increase in optic nerve tortuosity. Therefore, optic nerve length increase that we observed was not likely caused by general white matter swelling that could accompany a cephalad fluid shift, although any edema existing inflight may have dissipated by the time of the postflight MRI measurements.

Central sulcus narrowing and an upward brain shift are common findings in astronauts after long-duration flights.[11] The upward movement of the OC identified in the present study is consistent with these findings. In addition, MRI analyses postflight show shrinking of cerebrospinal fluid spaces at the convexities and increased ventricular cerebrospinal fluid volume.[11,24] The interpretations of these postmission findings are limited because measurements were done in 1-G, not inflight. Therefore, it is not clear whether the upward brain shift and OC displacement reflect the state of the brain in microgravity or whether these changes occurred after flight.

Study Limitations

The results in this study are convincing for microgravity-induced structural eye changes, but it must be acknowledged that no inflight MRI measurements were available. The ICP and pressures within the cerebrovascular system are likely different in weightlessness compared with the supine position on Earth.[25] For example, the brain has been shown to shift upward during head-down tilt, but with head-down tilt, there is a headward gravitational gradient as well as hydrostatic increases in ICP and central venous pressure.[26,27] None of this likely occurs in weightlessness. Instead, weightlessness is initially characterized by lower central venous pressure and ICP compared with supine and no headward hydrostatic gradients exist.[21,25] Also, blood volume is reduced in space.[28-30] When an astronaut returns to Earth, a major readaptation to weightlessness occurs. In the supine position, intracranial contents experience a fluid shift with hydrostatic gradients reintroduced for the first time in several months. Central venous pressure is increased,[31] and ICP likely increases as well. Over time, blood volume is restored.[29] Considering all the changes that take place during the readaptation to 1-G it is difficult to conclude whether MRI findings taken a median of 6 days after the flight still reflect the situation in flight. However, the ONH findings are related to mission length and correspond with the in-flight SANS manifestations, supporting that they are related to microgravity, whereas the OC findings are not related to mission length and could potentially be a postflight event. Furthermore, the significant correlation between anterior ONH movement (Table 3) and change in globe axial length indicates a direct relationship with the well-documented microgravity-induced globe flattening.

In addition to the uncertainty of extrapolating postflight findings to inflight, other limitations of this study include the small sample size and that some astronauts had previous spaceflights. Such previous exposure to microgravity could have residual effects on the eye, brain, and optic nerve that change the response to new spaceflights. Also, the heterogeneous clinical presentation of SANS makes it challenging to perform statistical inferences relating brain changes with ocular symptoms. In this study, this issue was addressed by lumping ocular findings into 1 single binary parameter. A possible downside to our approach is that subclinical changes are not included. Thus, taken together with the small sample size, any lack of association (e.g., the lack of association between the OC superior shift and SANS) cannot entirely rule out the possibility that a cause—effect relationship exists between the observed variables.

Additional important methodological limitations concern limited spatial resolution and the difficulties associated with obtaining an accurate centerline representation of the optic nerve, something that may lead to the false rejection of some changes and associations. Although the optic nerve ends were easily identifiable, it was more challenging to track the optic nerve through the orbital apex, something that likely added undesired variability to the length estimations. Therefore, although we did not observe a change in tortuosity (Table 2), some level of undetected straightening could have contributed to what we recorded as an optic nerve length increase. Of note, uncertainties in the positioning of the optic nerve ends should not interact with pre- or postspaceflight status of the images, and such uncertainties are therefore unlikely to introduce a change that in reality did not occur.

Altogether, our results show a spaceflight-induced optic nerve length increase and an anterior movement of the ONH that support that SANS is caused by an altered pressure difference between the brain and the eye leading to a forward push on the posterior part of the eye. To verify the implicated mechanism behind the ocular findings in SANS requires the direct assessment of ICP in space.

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Footnotes and Disclosures

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[1] Department of Radiation Sciences, Umeå University, Umeå, Sweden.

[2] Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden.

[3] Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire.

[4] Department of Clinical Science, Umeå University, Umeå, Sweden.

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HUMAN SUBJECTS: Human subjects were included in this study. The study adhered to the tenets of the Declaration of Helsinki and was conducted in conformance with the International Conference on Harmonization E6 guideline for Good Clinical Practice or the laws and regulations of the country in which the research was conducted. Committee for the Protection of Human Subjects (IRB) at Dartmouth College and the regional ethical review board in Umeå approved the study. The research was also approved by the IRB at NASA and use of the data was approved by the Lifetime Surveillance of Astronaut Health (LSAH) program. All participants provided informed consent.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Wåhlin, Malm, Buckey, Eklund

Data collection: Wåhlin, Holmlund, Fellows, Buckey, Eklund

Analysis and interpretation: Wåhlin, Holmlund, Fellows, Malm, Buckey, Eklund

Obtained funding: Buckey, Eklund

Overall responsibility: Wåhlin, Holmlund, Fellows, Malm, Buckey, Eklund

Abbreviations and Acronyms:

ICP = intracranial pressure; **IIH** = idiopathic intracranial hypertension; **IRB** = Institutional Review Board; **ISS** = International Space Station; **MRI** = magnetic resonance imaging; **OC** = optic chiasm; **ONH** = optic nerve head; **SANS** = spaceflight-associated neuro-ocular syndrome.

Key words:

microgravity, optic nerve, magnetic resonance imaging, space, idiopathic intracranial hypertension, spaceflight-associated neuro-ocular syndrome, Papilledema, intracranial pressure.

Correspondence:

Anders Eklund, PhD, Department of Radiation Sciences, Umeå University, 901 85 Umea, Sweden. E-mail: anders.eklund@umu.se.

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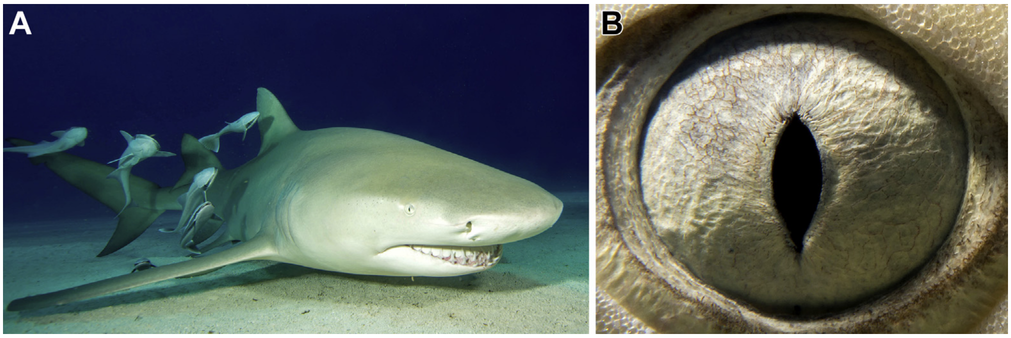
Pictures & Phylogeny



Vertical Pupil in a Lemon Shark

The lemon shark (*Negaprion brevirostris*) (Fig **A**) is mainly piscivorous, coastally distributed, and mostly found in the Western Hemisphere. Its startling vertical slit pupils (Fig **B**) are generally found in predators, with horizontal pupils being found in prey species. There are many theories regarding the value and purpose of such pupils including correction of chromatic aberration, response to various levels of illumination, improvement of astigmatic depth of field, and multifocality. Lemon shark eyes have a visual streak of concentrated photoreceptors, including both rods and cones in the horizontal meridian, although its functional interaction with the pupil is not understood. Photos taken in the Bahamas by David G. Heidemann (Magnified version of Fig **A**-**B** is available online at www.aaojournal.org).

Ivan R. Schwab, MD[1]
David G. Heidemann, MD[2]

[1]University of California, Davis, California; [2]William Beaumont School of Medicine, Royal Oak, Michigan