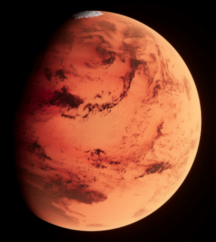
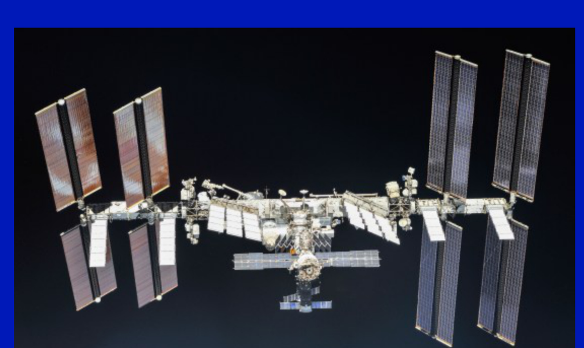


MARS. The average distance is about 225 million kilometers (140 million miles). Travel time approximately 150-300 days. Gravitational force is about 38% of that on Earth.

MOON. The average distance is about 384,400 kilometers (238,855 miles). Travel time approximately 3 days. Gravitational force is approx. 1/6 of that on Earth.

ATMOSPHERE. Layers reaching outwards 10,000 kilometers (6,214 miles) beyond Earth's surface. ***Did you know*** that the atmosphere protects life on Earth from UV radiation, maintains temperature and breathable air, creates wind and weather patterns that distribute heat and water around the globe.



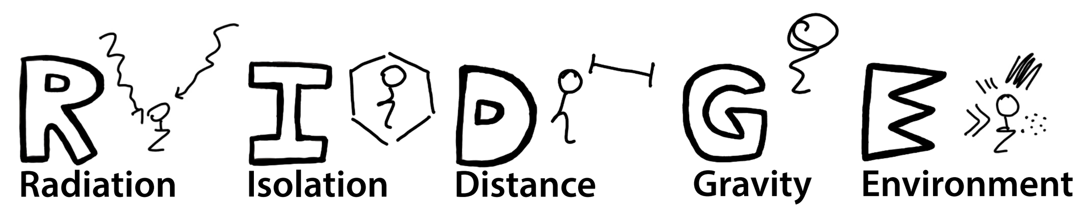
ISS. The International Space Station orbits Earth at an average altitude of 420 kilometers (about 260 miles). Travel time varies, averaging 6 hours. Gravitational forces about 90% of those on Earth.

EARTH. We are here. Force of gravity is 9.8 m/s^2.

ELECTROPHYSIOLOGY IN MICROGRAVITY

Astronaut Health Hazards

The results are in, planet Earth remains the most hospitable place for humankind. In space, several factors negatively effect human health. These factors include: high-energy particle radiation, a sense of boredom, fluctuation of morale, prolonged communication times, resource scarcity, an inability to *stand up*, high stress levels, and a crowded visual environment, to name a few.



MICROGRAVITY

The lack of gravity has tremendous repercussions on the physical body. Astronauts may experience difficulty with balance, hand-eye-coordination, and motion sickness. Without gravity there are no weight-bearing exercises, so astronauts can expect to lose 1-1.5% of bone mass per month in space. This change in mineral density leaves calcium in the blood which may cause kidney stones.

Most notably, there is a complete inability to *stand up* while in microgravity. Changing body position from laying to sitting or standing does the service of shifting fluids throughout the body. In a state of perpetual weightlessness, an observable headward fluid shift occurs.

HISTORY of HUMANS IN SPACE

1961 was the year of the first human space travel. Humans first walked on the moon in 1969 during the Apollo 11 mission. In 2000 the International Space Station (ISS) was completed; since then, there has been a consistent human presence in outer space.

Fun Fact: The ISS orbits Earth at a speed of 8km (5 miles) per second! It makes 16 orbits around the Earth over the course of 24-hours, that's one full orbit every 90 minutes!

LONG DURATION SPACEFLIGHT

Astronauts who work on the ISS typically spend multiple months in space. To date, the longest single spaceflight duration was 437 days, 18 hours, and 22 minutes. Conversely, a Mars mission would take 3 years to complete!

Diagnosys in Space

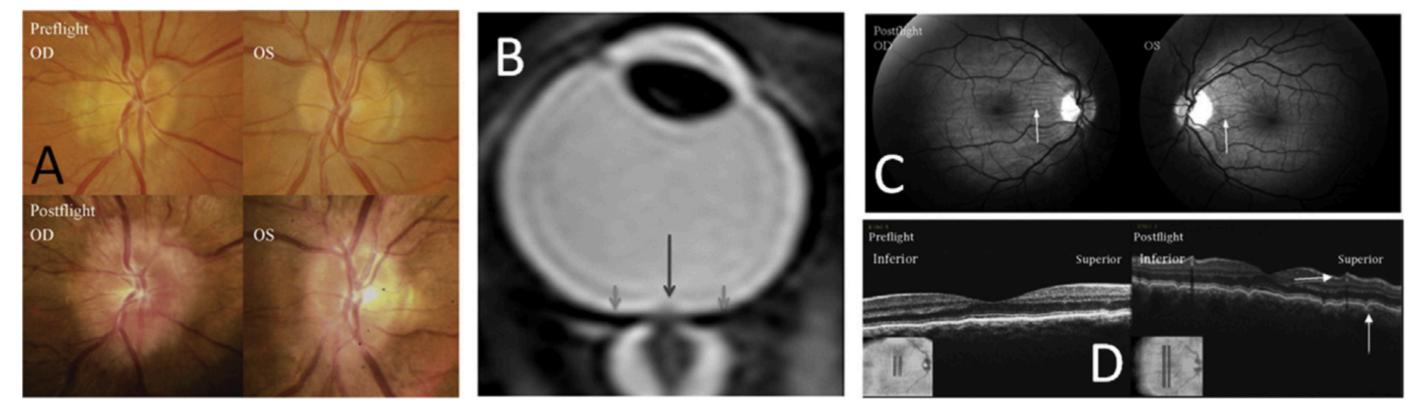
On August 10th 2021, NASA launched an E3 system with Envoy and ColorBurst to the ISS. This system was placed into service in early 2022 and was first used to test an ISS crew member in April 2023, marking the first time in history that human electroretinography (ERG) was conducted in space.

Notably, the E3 system needed no modifications to survive a rocket launch or to conduct quality testing in the unique electrical noise environment that is the ISS.

Spaceflight Associated Neuro-ocular Syndrome (SANS)

A condition attributed to long-durations in microgravity

The first report of spaceflight vision problems was difficulty reading checklists. Shortly thereafter, an investigation was launched to examine vision changes. This condition was originally named Visual Impairment and Intracranial Pressure (VIIP). However, increased intracranial pressure was shown not to be the primary driver, and thus the name was changed to Spaceflight Associated Neuro-Ocular Syndrome (SANS).



The symptoms most commonly associated with SANS are optic disc edema, globe flattening, choroidal folding, and hyperopic shift. Although most astronauts are asymptomatic, approximately 70% develop symptoms of SANS, and approximately 66% present with optic disc edema. Risk factors are unknown, although cup to disc ratio and other potential predispositions are under investigation. It is also unclear if eye changes are reversible.

WHAT ABOUT INTRAOCULAR PRESSURE (IOP)?

IOP increases by 50 - 100 % upon initial entry into orbit. This change lasts between 24 - 48 hours, after which intraocular pressure drops back to normal range. Tonometers are used onboard to monitor changes.

HOW DOES SANS RELATE TO INTRACRANIAL HYPERTENSION (IIH)?

SANS lacks key symptoms consistent with IIH, including: chronic headache, pulse-synchronous tinnitus, and diplopia. While both SANS & IIH produce optic disc swelling, displacement directions vary. In IIH, the optic nerve head moves anteriorly, while in SANS, displacement is more frequently posterior. Both present with choroidal and retinal folding, however, SANS more frequently creates choroidal and IIH retinal folding patterns.

SANS Investigational Tools

ONBOARD THE ISS

Fundoscopic imaging: optic disc edema, cotton wool spots, choroidal & retinal folds

Ocular ultrasound: posterior globe flattening

OCT: total retinal thickness, retinal nerve fiber layer thickness, choroidal & retinal folds

ERG: optic nerve function: PERG central 20 degrees, PhNR full field - findings yet to be reported

TERRESTRIAL ONLY

MRI: posterior globe flattening

Lumbar puncture: opening pressures

Electrophysiology on the ISS

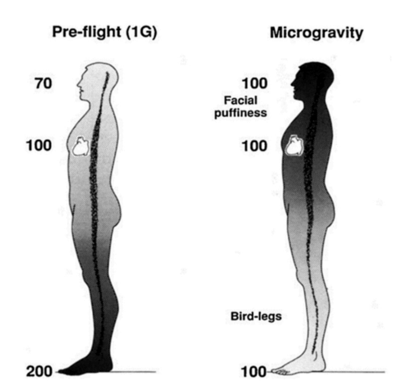
Optic nerve function is now incorporated into routine testing

Pattern ERG (PERG) and photopic negative response (PhNR) tests are now included as routine eye exams for astronauts before, during, and after spaceflight.

Thus far we know that: early studies found decreased optic nerve function during the head down tilt analog model. PhNR is reduced in patients with glaucoma, optic neuropathy, and optic neuritis. And, PhNR appears to be a useful index of optic neuropathy in a group of individuals with IIH. As for electrophysiology in space, we will wait and see what this new frontier holds!

The fluid shift hypothesis

The leading hypothesis for the etiology of SANS is the fluid shift hypothesis. Simply put, prolonged exposure to microgravity wreaks havoc on normal circulation and fluid drainage. Because the human body is designed to pump blood to the head against the force of gravity, without gravity, fluids pool and stagnate. This excess of fluid disturbs the pressure gradients between interstitial fluid, lymphatic vessels, and veins. Without the option to "stand up" or "sit up", these fluids do not drain as they do on Earth.



Hydrostatic forces can help to explain this hypothesis. Hydrostatic forces are the pressure exerted on a fluid by the weight of the fluid above it. The formula is: $P=\rho gh$, where P is the pressure, ρ (rho) is the density of the fluid, g is the acceleration due to gravity, and h is the height of the fluid column above the point in question. When standing up, the feet have higher blood pressure than the head, while laying down, blood pressure equalizes across the length of the body. However in microgravity, bodily blood pressures are constantly equal to that of a supine position.

EVIDENCE FOR FLUID SHIFT HYPOTHESIS

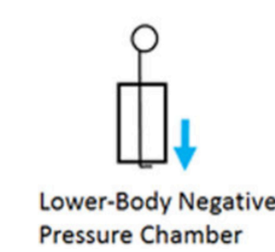
1. Plethysmography was used to measure the change of fluid volume in different parts of the body. This demonstrated that 2 Liters of fluid moved from the legs to the thorax during spaceflight.
2. Ultrasound images revealed that the internal jugular veins of astronauts during short-duration spaceflight increased by 40% in cross-sectional area relative to the seated posture on Earth. During long-duration ISS missions, internal jugular vein volume increased by as much as 200% compared to preflight supine values.
3. Upon entering weightlessness, astronauts report symptoms of "Space Adaptation Syndrome" which include facial edema, headaches, and dizziness. Without a gravitational gradient fluids shifts toward the head while also decreasing fluid volume in the limbs. This has gained the endearing nickname, "puffy head bird legs".

GROUND ANALOGS

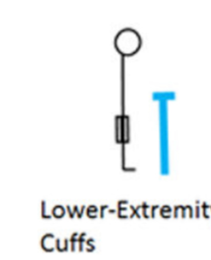
Several ground analogs have been developed, of which strict head-down tilt bed rest can reproduce edema and retinal folding akin to SANS. Study participants must lay supine on a 5-degree incline for 30- to 60-days. Any head lifting movement during eating or otherwise will drain the fluids, so participants must maintain a very strict head-down posture at all times.

Countermeasures

The best countermeasure is to come home and stand upright



Lower body negative pressure (LBNP) chambers create a vacuum suction effect on the lower extremities to draw in and sequester fluids in the venous system. One study, however, demonstrated that LBNP was not effective at reducing choroidal thickening. Current LBNP devices are large and immobile requiring a new design, or the option to use it during sleep. Frequency and duration have not been established.



Lower extremity venoconstrictive thigh cuffs (VTCs) apply pressure to the femoral veins, trapping venous blood in the legs, away from the upper body. VTCs have shown to reverse elevated IOP and choroidal thickening induced in Earth analog models. This method is currently used to decrease symptoms of "head congestion". Crew members can move freely with VTCs.

Space anticipation glasses are available onboard, though only 2 diopter shift.

Acetazolamide is on the Space Station, but has never had to be used.

References

Brunstetter T, Huang A, Laurie S, Lee AG, Karanjia R, Macias B. "Neuro-Ophthalmic Manifestation of Space Acquired Neuro-Ocular Syndrome (SANS)." NANOS, 2 March 2024, Honolulu, HI. Lecture symposium.

Cranford N, Turner J. "The Human Body in Space." NASA. 2 February 2021. https://www.nasa.gov/humans-in-space/the-human-body-in-space/

Huang AS, Stenger MB, Macias BR. Gravitational Influence on Intraocular Pressure: Implications for Spaceflight and Disease. *J Glaucoma*. 2019 Aug;28(8) 756-764. doi:10.1097/ijg.0000000000001293. PMID: 31162175; PMCID: PMC6786882.

Moss HE, Park JC, McAnany JJ. The Photopic Negative Response in Idiopathic Intracranial Hypertension. *Invest. Ophthalmol. Vis. Sci.* 2015;56(6):3709-3714. https://doi.org/10.1167/iovs.15-16586.

Spaceflight Associated Neuro-ocular Syndrome (2022). Elsevier Academic Press.

Stern C, Yucel YH, Eulenburg P, et al. Eye-brain axis in microgravity and its implications for Spaceflight Associated Neuro-ocular Syndrome. *npj Microgravity* 9, 56 (2023). https://doi.org/10.1038/s41526-023-00300-4